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## SYMPOSIUM ON RECENT ADVANCES IN TREATMENT

The following clinics are included in this Symposium

Paul D. White and R. Earle Glendy RECENT ADVANCES IN THE TREATMENT OF HEART DISEASE.

Soma Weiss RECENT ADVANCES IN THE TREATMENT OF ARTERIAL HYPERTENSION

Chester S. Keefer THE TREATMENT OF GONOCOCCAL ARTHRITIS RHEUMATOID ARTHRITIS AND GOUT

J. H. Meigs TREATMENT OF DISEASES OF THE THYROID

Conrad Weselhoeft TREATMENT OF SCARLET FEVER AND DIPHTHERIA.

LeRoy D. Fothergill SOME RECENT ADVANCES IN VACCINES AND SERUMS A REVIEW

Joe Vincent Meigs RECENT ADVANCES IN MEDICAL GYNECOLOGY

Abraham Colmes RECENT ADVANCES IN THE TREATMENT OF HAY FEVER AND ASTHMA.

Edward S. Emery, Jr. RECENT ADVANCES IN DIETOTHERAPY



CLINIC OF DRS PAUL D WHITE  
AND R EARLE GLENDY

FROM THE CARDIAC CLINICS AND LABORATORY OF THE MASSA-  
CHUSETTS GENERAL HOSPITAL

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RECENT ADVANCES IN THE TREATMENT OF HEART  
DISEASE

INTRODUCTION

DURING the past decade several significant advances have been made in the treatment of heart disease, probably more than in any previous decade. We have selected for presentation herewith, 5 cases, each illustrating one of the more important new therapeutic measures. In the order of discussion these five measures are quinidine therapy, the use of salyrgan or mercupurin, paravertebral alcohol injection, total thyroidectomy and pericardial resection. They are important adjuncts in treatment but by no means replace any of the reliable older methods of cardiac therapy which include rest, restriction of fluids and diet, the proper use of digitalis, of vasodilator drugs, and of diuretics by mouth, and the cardiac bed and Southey tubes, merely to mention the more important time-honored methods.

One other new therapeutic measure which deserves honorable mention at least, even if not so important as those that are presented in detail in this report, is the administration of theophyllin-ethylene-diamine (ordinarily called aminophyllin, euphyllin, or metaphyllin) in the relief of Cheyne-Stokes respiration and obstinate recurrent angina pectoris (especially at rest). In such cases rapid and striking relief may sometimes follow the administration of  $7\frac{1}{2}$  grains (2 cc. ampule) of aminophyllin intramuscularly, or 4 grains (10 cc. ampule) intravenously, or less satisfactorily  $1\frac{1}{2}$  to 3 grains by mouth, two to five times daily.

## QUINIDINE THERAPY

Case I—J L, a Jewish boy aged nineteen years, was admitted to the Massachusetts General Hospital on February 28, 1935, complaining of rapid irregular palpitation and some vomiting of four months' duration. He had had whooping cough and measles in childhood. In May, 1925, several months after an infection with fever and vomiting, he was seen by us and found to have rheumatic heart disease, with well-marked cardiac enlargement, mitral stenosis, aortic regurgitation, and a normal rhythm with a rate of 96 beats per minute. In June, 1925, a tonsillectomy was done. In the fall of 1925, on account of persistent signs of rheumatic activity (increased temperature, pulse, and white blood cell count), he was put to bed and kept there for about six months, during which time he continued to have a rapid pulse rate, at times as high as 140. From June, 1926 to November, 1934 he felt fairly well, except for an occasional respiratory infection, and with restricted activity was able to attend school and lead a fairly normal life. His heart gradually increased in size, but the rhythm remained normal. During November, 1934, following a cold, he noticed, for the first time, rapid irregular palpitation. He was digitalized at this time and given a maintenance dose of digitalis. For the next three months he did not feel well. On the days when the palpitation was most noticeable he felt weak and often vomited almost everything eaten. Early in December, 1934 he spat  $\frac{1}{2}$  ounce of bright red blood, and two weeks later again raised the same amount of blood. From that time until his admission to the hospital, he was confined to bed and chair except for an occasional short walk. The distressing palpitation continued. There was no dyspnea, orthopnea, or edema. His physician referred him to the hospital because of a persistently rapid pulse rate, which did not respond even to large doses of digitalis and small doses of quinidine at home.

Physical examination showed a fairly well nourished, somewhat pale young man with anxious facies sitting propped up in bed. Breathing was slightly rapid. There were rapid irregular arterial pulsations in the neck. The pupils were somewhat dilated but reacted normally. There were a few slightly enlarged nontender axillary lymph glands. The precordium bulged slightly. The heart was greatly enlarged downward and to the left, the left border of dullness lying in the midaxillary line. The apex impulse was forceful and easily visible in the seventh interspace. The first sound at the apex was slapping in quality and preceded by a mid- and late-diastolic rumble. There was also a short systolic murmur at the apex. Along the left sternal border a faint early blowing diastolic murmur was audible. The rhythm was totally irregular at a rate of 160 beats per minute. The blood pressure was 154 mm mercury systolic and 20 diastolic. The liver was palpable 4 cm below the costal margin in the nipple line. There were no rheumatic nodules and no cyanosis or edema.

The urine was normal on two occasions. The hemoglobin was 80 per cent (T), the red blood cell count was 5,220,000 and the white count was 21,430. The corrected sedimentation rate was 0.57 mm per minute. The Hinton reaction was negative. The electrocardiogram showed auricular fibrillation with a ventricular rate varying from 120 to 180. The basal metabolic rate on six occasions, after his rapid pulse rate was controlled, ranged from -1 per cent to -19 per cent, three times less than -10 and three times greater than -10.

The accompanying chart (Fig 164) shows his course while in the hospital, including temperature, apex and radial pulse rates, respirations, medications, sedimentation rate, and white blood cell counts. Digitalis was discontinued

on the second day because of nausea. It was not certain whether he had had too much digitalis or was simply nauseated from congestion in the gastrointestinal tract. On the morning of the third day after admission following the administration of 30 grains of quinine sulphate in divided doses of 6 grains each in twenty four hours for two days, the pulse rate dropped from 130 to 80 beats per minutes and the rhythm became fundamentally regular, with much subjective relief of symptoms. Thereafter, while in the hospital, the pulse rate ranged from 80 to 90 occasionally rising to 100 or slightly above. The slight discrepancy in apex and radial rates after the auricular fibrillation ceased was due to premature beats. On account of evidence of ac

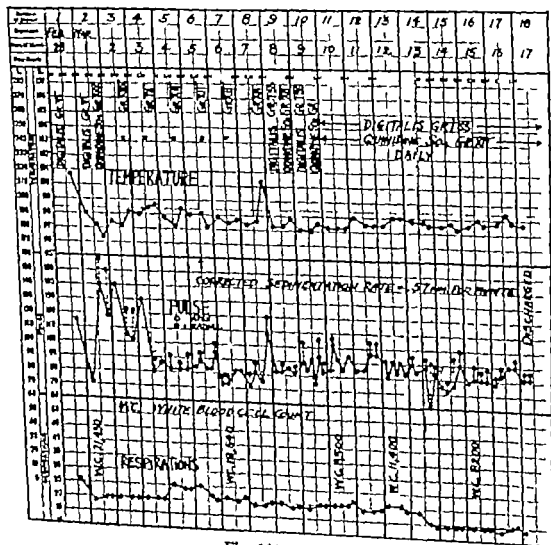


Fig 164.—Case I

live rheumatic infection, which no doubt, made the auricular fibrillation so refractory to treatment, he was kept quietly in bed and advised to remain in bed for several weeks on his return home. He was discharged much improved on a ration of  $1\frac{1}{2}$  grains of digitalis and 12 grains of quinine sulphate daily in divided doses of 3 grains each. His basal metabolic rate on one occasion after leaving the hospital was plus 30 per cent. This was checked with total thyroidectomy in mind as a possible therapeutic procedure.

He was last seen on September 6, 1935 five months after his discharge from the hospital. Following his discharge he remained quiet for several weeks and continued on a daily ration of digitalis,  $1\frac{1}{2}$  grains, and quinine sulphate

3 grains, four times a day, for nearly three months. He improved remarkably and was able to work almost every day through the summer as an announcer at an amusement park. The digitalis was omitted and the dosage of quinidine sulphate reduced to 6 grains daily, 3 grains in the morning and 3 grains at night.

Physical examination on September 6, 1935, showed his skin well tanned and his general condition good. The apex impulse of the heart was visible and palpable in the seventh intercostal space 12.5 cm to the left of the mid-

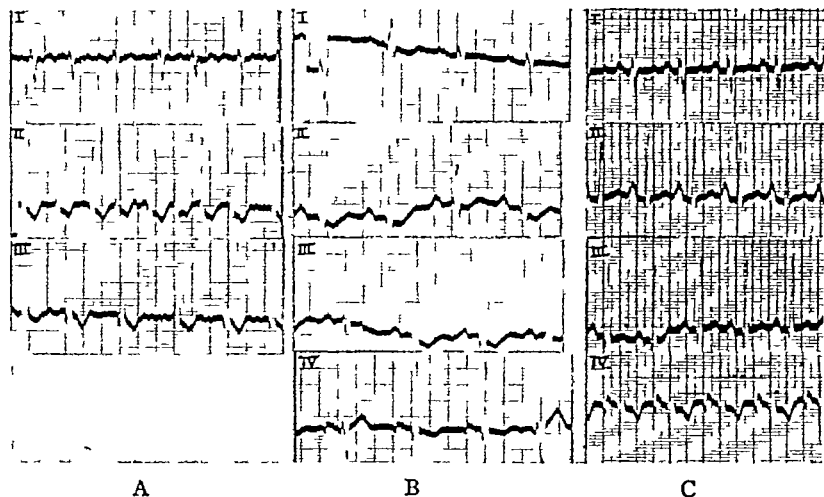


Fig 165—Case I A, February 28, 1935 Fully digitalized but before intensive quinidine therapy Auricular fibrillation, ventricular rate 120–180, well-marked right axis deviation, and deeply inverted S-T segments in Leads II and III B, March 3, 1935 After quinidine sulphate in divided doses of 6 grains each five times a day for two days (60 grains in all) Normal rhythm, rate 80, interrupted every third beat by an abnormal QRS complex, probably a late premature beat Prolonged P-R interval (0.23 seconds), right axis deviation, and persistent digitalis effect upon the S-T segments C, September 6, 1935 After a fairly active summer No digitalis for several months Quinidine sulphate, 3 grains, twice daily, morning and night Normal rhythm, rate 100, slightly prolonged P-R interval (0.21 seconds), prominent P<sub>2</sub>, low but upright T waves in the conventional leads (disappearance of digitalis effect), and right axis deviation

sternal line. There were moderate aortic systolic and diastolic murmurs, a slight to moderate apical middiastolic murmur, and a loud apical systolic murmur. The blood pressure was 140 systolic and 60 diastolic. The lungs were clear, the liver was not enlarged, and there was no edema over the shins or ankles. He was advised to carry on quietly, using 3 grains quinidine, twice daily, or more often if necessary, and, if possible, to spend the winter in a milder climate.

Figure 165 shows serial electrocardiograms during and following the auricular fibrillation.

**Discussion.**—So long ago as 1749 quinine was reported by Senac to be helpful in the control of rebellious palpitation, but it was used very irregularly and by most internists not at all, until about fifteen years ago, when its isomer quinidine was introduced by Frey,<sup>1</sup> after he had learned of the accidental discovery (by a patient of Professor Wenckebach's) of the beneficial effect of quinine in controlling paroxysmal auricular fibrillation.

Fifteen years ago quinidine was tried out in a large number of unselected cases of auricular fibrillation. Frequently it restored normal rhythm, but there were many failures and a few disasters which resulted in considerable dissatisfaction or actual fear in the use of the drug.

During the past ten years, however, in carefully selected cases, quinidine sulphate has been found useful and, at times, even life saving, as in our Case I, recounted above, who undoubtedly would have gone on to extensive congestive failure and death had there been a persistence of the uncontrolled ventricular rate in his obstinate auricular fibrillation.

There are three indications for quinidine therapy. In the first place it may save lives by the restoration of normal rhythm in cases of auricular fibrillation or paroxysmal ventricular tachycardia in the presence of serious heart disease (including coronary thrombosis) when other measures have failed. Secondly, it may restore normal rhythm in cases of persistent auricular fibrillation who show little or no heart disease, especially when they are uncomfortable as a result of the palpitation caused by the arrhythmia. And thirdly, in rations it may prevent disturbances of rhythm, particularly paroxysms of auricular fibrillation and also sometimes paroxysmal tachycardia and premature beats.

For the control of auricular fibrillation or paroxysmal ventricular tachycardia a good method of quinidine treatment has, in our hands, been to administer 6 grains of quinidine sulphate every two hours for five doses on a given day following a test dose of 3 grains (to detect any unusual sensitivity to the drug). This program of 30 grains of quinidine sulphate divided into five doses over a period of eight hours usually suffices to restore normal rhythm, but if the abnormal rhythm persists the program can be extended cautiously to include



one to two more doses in two to four hours, or it may be repeated the next day. Patients receiving these large doses of quinidine sulphate should be in bed under close observation and preferably with electrocardiographic control (for example, an electrocardiogram should be taken before starting quinidine, before the third dose, and before the fifth dose). Mild toxic symptoms such as slight tinnitus are not important, but severe symptoms of cinchonism, excessive tachycardia (over 150 per minute), or intraventricular block by electrocardiogram demand the omission of the drug.

Finally in the prevention of arrhythmias, rations of 3 or rarely 6 grains of quinidine may be taken one to four times a day (even at three hour intervals) for periods of days or weeks. The effect of a single dose lasts about four hours. Therefore, it is important to prescribe quinidine an hour or so before some particular effort or episode which might excite an attack of tachycardia or fibrillation. Looseness of the bowels (sometimes a favorable laxative effect) or a little deafness occasionally results from the long continued use of quinidine sulphate and may require omission of the drug or reduction in the dosage.

### SALYRGAN

**Case II.**—A E B, a seventy-one-year-old merchant, till June in good health, was admitted to the Baker Memorial Hospital in September, 1932. His first serious symptoms had appeared three months previously while driving his car home from a family dinner. At the onset he complained of indigestion. After several hours he vomited and later developed a feeling of pressure in his chest and difficulty in breathing. He preferred to sit upright by the open window. He coughed and raised blood-tinged sputum. Respiration was wheezing in character. He remained strictly in bed for several days following this episode and had spent the greater part of his time in bed thereafter, though he drove his car on two occasions. Approximately nine weeks after the onset of symptoms he was found in a stuporous condition, thought to be uremic coma, from which he recovered in a few days. Coincidentally edema of the legs appeared and breathing became increasingly more difficult up to the time he was seen by us, in spite of a fair amount of digitalis and diuretics by mouth.

Physical examination revealed an elderly man who apparently had lost weight but who showed extensive edema of the legs, genitalia, and trunk. Breathing was somewhat rapid and labored. The pupils reacted normally. The upper teeth were replaced by a denture. Many lower teeth were missing. The tongue and buccal mucous membrane were bright red and moist, the tongue was sore. The heart apex and left border of dullness were in the sixth intercostal space, 13 cm from the midsternal line and well outside the mid-clavicular line. The heart sounds were of poor quality, the rhythm was regular except for an occasional premature beat, the rate was 86 beats per minute,

and there were no murmurs. The blood pressure was 128 mm mercury systolic and 98 diastolic. There was evidence of a considerable quantity of fluid in the right chest, and many moist rales were found in the left lower lung. The liver was enlarged extending 6 cm below the costal margin, and there was moderate ascites.

The urine on several occasions showed the slightest possible trace of albumin and several white and red blood cells. The specific gravity varied from 1.014 to 1.016. The nonprotein nitrogen of the blood was 34 mg per cent. The hemoglobin was 75 per cent (T), the red blood count was 5,050,000, and the white count was 12,700. The differential count and smear were normal.

The electrocardiogram showed ventricular premature beats interrupting an otherwise normal rhythm, rate of 90, P-R interval prolonged 0.22 second, slightly slurred Q-R-S waves, and low T waves.

The severe congestive failure was thought to be the result of long standing hypertension and attendant coronary disease. The prognosis was considered quite grave and it seemed that even with the best treatment his anasarca could be but temporarily controlled.

The accompanying chart (Fig 166) shows at a glance the extensive therapy he received while in the hospital, including venesection, thoracentesis, digitalis, the xanthine diuretic theocalcin and the mercurial diuretic salyrgan. His response to treatment was far beyond expectations and as the hydrothorax and edema cleared he improved gradually. Near the end of his hospital stay he was able to be fairly active, walking about without dyspnea and free of edema except for very slight pitting of both feet posteriorly.

Following his discharge from the hospital on December 14, 1932, after an eleven weeks' stay, he did fairly well at home under a quiet régime, a maintenance dose of digitalis, and salyrgan two or three times a month. A constant low grade of congestive failure persisted, however, and varied with the response to diuretics.

One year following the onset of his original symptoms he was admitted to the hospital again on account of increasing congestive failure, weakness and mental confusion. At this time he was quite dyspneic, and the respirations were of the Cheyne-Stokes variety. The lips and tongue were cyanotic. The cervical and arm veins were engorged. The heart apex impulse and left border of dullness were 12 cm. to the left of the midsternal line in the sixth intercostal space. There was a slight gallop rhythm at the apex and marked slowing of the heart rate with audible auricular sounds during the periods of hyperpnea, probably the result of an increase in A-V block (shown to be present by electrocardiogram). The pulmonary second sound was slightly accentuated. There were no murmurs. The blood pressure was 130 systolic and 80 diastolic. There was a moderate amount of fluid in the right chest and in the abdomen. The liver was engorged and palpable, 6 cm. below the costal margin. There was edema over the flanks and of the ankles. The electrocardiogram showed an unusual ectopic auricular tachycardia at a rate of 170 with varying degrees of A-V block (2:1 and 4:1) and a ventricular rate ranging from 42 to 84, also low voltage and a rare ectopic ventricular beat. The urine on two occasions showed a very slight trace of albumin and a low specific gravity (1.002 to 1.010). The blood counts and hemoglobin were normal. The nonprotein nitrogen of the blood was 44 mg per cent on admission and 32 mg per cent one week after admission.

His treatment on this occasion was, for the most part, as it had been previously (rest, digitalis, theocalcin, and salyrgan). His response was good to the extent that his edema cleared but he remained quite weak and mentally

one to two more doses in two to four hours, or it may be repeated the next day. Patients receiving these large doses of quinidine sulphate should be in bed under close observation and preferably with electrocardiographic control (for example, an electrocardiogram should be taken before starting quinidine, before the third dose, and before the fifth dose). Mild toxic symptoms such as slight tinnitus are not important, but severe symptoms of cinchonism, excessive tachycardia (over 150 per minute), or intraventricular block by electrocardiogram demand the omission of the drug.

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The accompanying chart (Fig 166) shows at a glance the extensive therapy he received while in the hospital, including venesection, thoracentesis, digitalis, the xanthine diuretic theocalcin and the mercurial diuretic salyrgan. His response to treatment was far beyond expectations and as the hydrothorax and edema cleared he improved gradually. Near the end of his hospital stay he was able to be fairly active, walking about, without dyspnea and free of edema except for very slight pitting of both feet posteriorly.

Following his discharge from the hospital on December 14, 1932, after an eleven weeks' stay, he did fairly well at home under a quiet régime, a maintenance dose of digitalis, and salyrgan two or three times a month. A constant low grade of congestive failure persisted however, and varied with the response to diuretics.

One year following the onset of his original symptoms he was admitted to the hospital again on account of increasing congestive failure, weakness, and mental confusion. At this time he was quite dyspneic and the respirations were of the Cheyne Stokes variety. The lips and tongue were cyanotic. The cervical and arm veins were engorged. The heart apex impulse and left border of dullness were 12 cm. to the left of the midsternal line in the sixth intercostal space. There was a slight gallop rhythm at the apex and marked slowing of the heart rate with audible auricular sounds during the periods of hyperpnea, probably the result of an increase in A V block (shown to be present by electrocardiogram). The pulmonic second sound was slightly accentuated. There were no murmurs. The blood pressure was 130 systolic and 80 diastolic. There was a moderate amount of fluid in the right chest and in the abdomen. The liver was engorged and palpable, 6 cm. below the costal margin. There was edema over the flanks and of the ankles. The electrocardiogram showed an unusual ectopic auricular tachycardia at a rate of 170 with varying degrees of A V block (2:1 and 4:1) and a ventricular rate ranging from 42 to 84, also low voltage and a rare ectopic ventricular beat. The urine on two occasions showed a very slight trace of albumin and a low specific gravity (1.002 to 1.010). The blood counts and hemoglobin were normal. The nonprotein nitrogen of the blood was 44 mg. per cent on admission and 32 mg per cent one week after admission.

His treatment on this occasion was, for the most part, as it had been previously (rest, digitalis, theocalcin and salyrgan). His response was good to the extent that his edema cleared but he remained quite weak and mentally

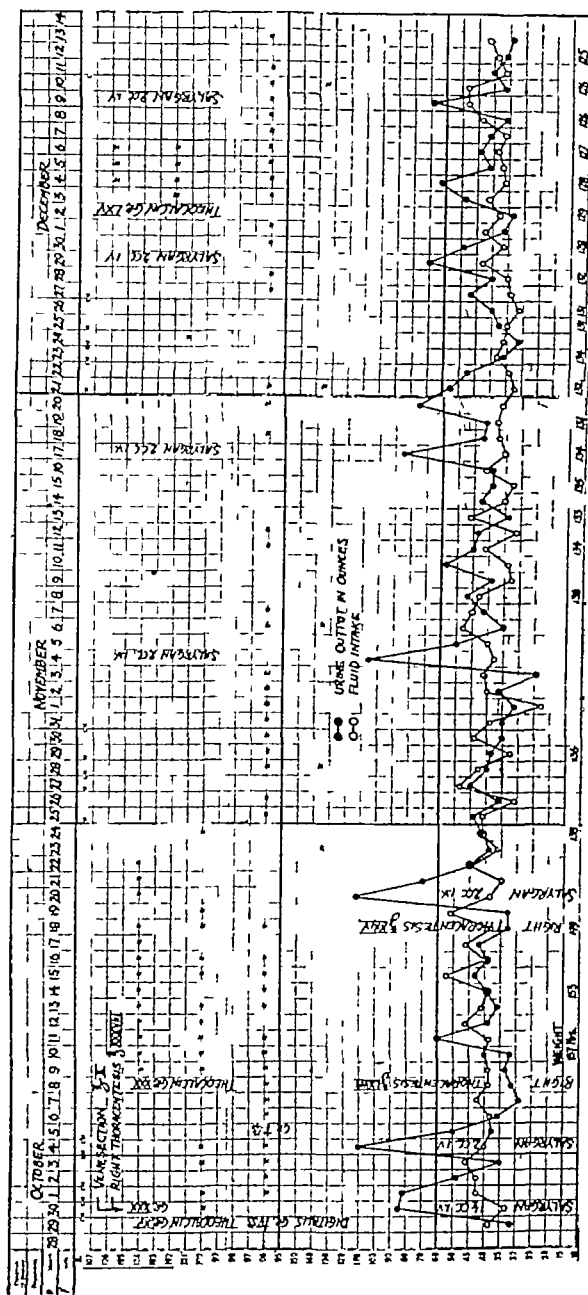


Fig 166—Case II

confused. He was discharged at the end of five weeks somewhat improved but his condition thereafter grew steadily worse and two weeks later he died of

progressive congestive failure and general debility after remaining in coma for two days. He survived longer than we had expected him to do when we first saw him

**Discussion**—Salyrgan or mersalyl, a preparation of mercury in solution for intravenous or intramuscular injection has proved a great boon in the last decade as a vigorous safe diuretic in the control of the intractable congestion due to heart failure or even other cause (such as chronic constrictive pericarditis, in preparation for operation) Its use is a refinement developed from the giving of mercury by mouth introduced many years ago for diuretic purposes and the accidental discovery by Saxl<sup>2</sup> in 1920 of the diuretic properties of mercury given intravenously to a syphilitic patient with edema. One of the original preparations novasural (merbaphen) was much less effective and more toxic. A newer preparation, mercupurin (novurit), has been introduced, which in a few patients is more effective than salyrgan and may be substituted for it in the same dosage. Mercupurin contains mercury and theophyllin which also acts as a diuretic.

Salyrgan by its favorable diuretic effect has prolonged lives in many cases of obstinate congestive heart failure and has at the same time made life more endurable. This was true in Case II, recounted above. It is best administered intravenously in a dosage of  $1\frac{1}{2}$  to 2 cc. with or without salt solution, great care being taken to avoid the spilling of any of the drug into the tissues around the vein or subcutaneously. If there is a leak of any of the salyrgan subcutaneously considerable pain and tissue destruction with ulceration are likely to occur. Intramuscular injection is safe but sometimes uncomfortable. This method may be used at the outset or in case the veins become thrombosed.

Salyrgan may be given at intervals of a few days or a few weeks as needed. It often is as effective after six months as it is the first day, and it rarely causes toxic symptoms or evidences of renal irritation. The urine should be watched with the latter possibility in mind. The drug is best given early in the morning, for its diuretic effect is most vigorous during the first twelve hours and thus the sleep of the patient is not interfered with. In a few cases where the diuretic effect of salyrgan or mercupurin is unsatisfactory diuretic salts may be given

by mouth for a few days previous to the administration of the mercury to enhance the effect, for example, ammonium chloride 15 grains (1 Gm) four times a day if tolerated

Some patients have been given an extraordinary number of injections of salyrgan over periods of a year or two, up to 100 injections or more. Also remarkable diuretic effects are seen occasionally, as much as 6 or 8 liters of urine in twenty-four hours

Finally, it is important to record the daily fluid intake and urinary output, and if possible to obtain the daily weight of patients receiving salyrgan

### PARAVERTEBRAL ALCOHOL INJECTION FOR ANGINA PECTORIS

Case III—H J, sixty-six years of age, formerly a professional weight lifter, was admitted to the Massachusetts General Hospital for the fifth time on April 29, 1935. His first admission had been ten years previously at which time he complained of typical attacks of angina pectoris of about one year's duration. He had also noticed at that time some dyspnea on effort, nocturnal dyspnea, and swelling of the feet. His past history was irrelevant except for an attack of "rheumatism" at the age of forty-three involving chiefly his ankles, and two eye operations, one for glaucoma, and the other for cataract. Physical examination on his first admission revealed an obese man with extensive arcus senilis in both eyes and fixation and irregularity of the pupil of the left eye from operative procedures. Many teeth were missing. Those remaining were dirty and carious. There was moderate pyorrhea alveolaris. The heart was enlarged to the left, the sounds were of poor quality, and there was a rough apical systolic murmur. The blood pressure was 110 mm mercury systolic and 50 diastolic. There were a few moist râles at the left lung base. The liver was palpable, 3 cm below the costal margin and slightly tender.

x-Ray examination of the heart in 1925 showed a well-marked increase in the total transverse diameter chiefly to the left, and a widened tortuous aorta. The electrocardiogram showed sino-auricular bradycardia, rate 48, and intraventricular block with left axis deviation. Examination of the blood was normal. The blood Wassermann reaction was negative. The nonprotein nitrogen of the blood was 35 mg per 100 cc of blood. The urine was normal on several occasions.

Following digitalis therapy and the removal of several abscessed teeth he showed moderate improvement and was discharged with a diagnosis of arteriosclerotic heart disease and angina pectoris. He was advised to continue with digitalis,  $1\frac{1}{2}$  grains daily, and to take potassium iodide, 10 drops three times a day.

He moved his place of residence and was not seen again for six years. In September, 1931 he returned complaining of frequent attacks of angina pectoris even when at rest. He was very nervous and reacted severely to his attacks of pain which made them totally incapacitating. The pain, for the most part, radiated to the left shoulder and down the left arm, but occasionally to the right shoulder and arm. On account of the crippling nature of his attacks which did not respond to the usual medical measures, paravertebral alcohol

(95 per cent) injection was advised and carried out by Dr J C White. The first, second third, and fourth dorsal sympathetic ganglia on the left were injected. Except for pleural pain incident to the injection and intercostal neuralgia for several weeks following the injection there were no complications. He was discharged on the tenth postoperative day considerably improved having had no substernal pain since the injection was made. The electrocardiogram at this time was essentially as previously described, the heart rate being 60.

Following the left-sided injection he had no further pain over the left precordium nor down the left arm. But as time went on he continued to have substernal oppression with radiation to the right side. This became quite as incapacitating as the pain which had previously radiated to the left side. Along with this were some symptoms and signs of myocardial weakness such as dyspnea on effort and at times a few rales at the lung bases, but never any gross evidence of congestive failure.

In May 1934, nearly three years after the left-sided alcohol injection he was admitted to the Massachusetts General Hospital again. On account of the continued severity of his symptoms alcohol injection on the right side was considered. However, injection of the first five dorsal sympathetic roots with novocain alone was tried first. This resulted in almost complete relief of pain for a period of about ten weeks following injection and justified a subsequent alcohol injection of the first second, and third right dorsal roots which was done a year later (April, 1935). Since that time to the present (December 1935) he has been much improved. No severe attacks of angina pectoris have occurred and he is able to keep relatively comfortable by using several nitroglycerin tablets daily to control the slight substernal discomfort which he experiences on effort.

**Discussion.**—Paravertebral alcohol injection for the relief of pain due to cardiac or aortic disease has become an established and useful method of treatment, particularly in cases of intractable angina pectoris and large aortic aneurysms. It has developed from the crude early attempts to relieve angina pectoris by cervical sympathectomy which was introduced by Jonnesco<sup>3</sup> in 1916. The development of our knowledge of the anatomy and physiology of the cardiac nerves has resulted in great improvement in the operative attack on angina pectoris. It is now possible to resect the nerves responsible for carrying the pain of angina pectoris to the central nervous system, namely, the first four or five dorsal rami communicantes on either side. Cervical sympathectomy is clearly recognized now as largely ineffective. However, the operation of dorsal sympathectomy is a difficult one and less advisable in most patients with angina pectoris than the much simpler but somewhat less accurate therapeutic measure of paravertebral alcohol injection.

In 1925 Mandl<sup>4</sup> introduced paravertebral novocain injection.



tion which gives temporary relief from angina pectoris Swetlow,<sup>5</sup> the following year, introduced paravertebral alcohol block of these same dorsal sympathetic rami communicantes. Since that time the technic of paravertebral alcohol injection for angina pectoris and for the pain of aortic aneurysm has been greatly developed by James C White.<sup>6</sup> In the last 20 cases treated in this way by White there has been no failure to obtain the desired effect.

The procedure is carried out under local anesthesia on the side in which most of the pain of the angina pectoris is located or to which it is referred. This is usually the left side. In occasional cases both sides have been treated in sequence at intervals of days, weeks, or months. Long needles are inserted paravertebrally, usually at the level of the first four dorsal nerve roots. Novocain is then injected and the determination is made forthwith of its effect on the sympathetic nerves (Horner's syndrome, dry warm hand, anesthesia over the left chest). If the proper effects result from the novocain, alcohol is then injected. For details of the procedure see White's recent monograph on the autonomic nervous system.<sup>6</sup>

Aside from the failure to reach the proper sites there may be a few minor hazards concerned, that is, irritation or penetration of the pleura, and intercostal neuritis. Successful cases have shown usually permanent relief from a large part of the pain or distress on the side injected. Usually there remains a warning sensation which keeps the patient's activity under control. This sensation is not pain but a feeling of something wrong.

The patients to be selected for this therapeutic measure are cases of obstinate angina pectoris who are miserable from the constant repetition of angina pectoris even when leading much restricted lives, who have not been helped by medical measures consisting chiefly of rest and vasodilating drugs, and who are not thought to be suitable cases for total thyroidectomy, and also a few cases with severe pain due to the pressure of large aortic aneurysms.

Paravertebral alcohol injection probably has no direct influence on the underlying disease process, namely, coronary atherosclerosis, nor on the duration of life, but it does make

life much more endurable in most patients and it may conceivably even add to the duration of life indirectly by reducing the reaction incident to angina pectoris itself. Very rarely the removal of the disagreeable symptom of angina pectoris has resulted in careless overactivity and the precipitation of a fatal heart attack.

### TOTAL THYROIDECTOMY FOR ANGINA PECTORIS

**CASE IV**—W G R., a sixty-seven year-old physician was first seen by us on April 7 1934. He had always been a vigorous worker and well and active except for appendicitis in childhood and a recurrence of this condition at the age of sixty two, requiring appendectomy. A ventral hernia resulted in 1922 and in 1923 respectively, each time when very tired, he had a cardiac arrhythmia, probably consisting of premature beats, which was relieved on both occasions by taking a vacation from his busy practice. His blood pressure was said to have been persistently low (90-100 systolic) for a number of years.

In 1932 he first noticed substernal oppression on walking fast after dinner. This symptom recurred infrequently and mildly thereafter whenever he hurried. In November, 1933 the trouble increased sharply in frequency and severity, coming on slight provocation. It was relieved by whisky, but more promptly by nitroglycerin. During February and March 1934, the pain which had previously always come on slight or moderate effort, had occurred on six occasions at night while at rest. He was bothered occasionally by palpitation but there was no dyspnea. His recent treatment had consisted of rest, omission of tobacco, euphyllin, and nitrites when necessary. These measures were not sufficient to control his symptoms. He slept poorly and was upset considerably by the serious illness of a relative.

Physical examination in April 1934 showed him to be well developed and of large build. He seemed tired and quite nervous. His breathing was normal. The skin was slightly pale. The pupils reacted normally to light and distance. There was no arcus senilis. The thyroid gland was not palpable. The teeth were all out and replaced by dentures. The tonsils were normal in appearance. There was no engorgement or abnormal pulsation of the neck vessels. The apex impulse of the heart was felt in the fifth interspace, 9 cm. from the midsternum in the midclavicular line. There was no abnormal dullness at the base or to the right of the sternum. The heart sounds were of good quality the rhythm was normal, the rate was 60, and there were no murmurs. The artery walls were soft. The blood pressure was 112 mm mercury systolic and 70 diastolic. The lungs were clear. The abdomen and extremities were normal.

On fluoroscopic examination the heart was found to be slightly enlarged and the aorta somewhat tortuous. The electrocardiogram showed normal rhythm rate of 80 and upright T waves in the three classical leads.

A diagnosis of coronary heart disease with angina pectoris was made. Normal activity seemed limited to the extent of 75 per cent by his cardiac condition and the prognosis was regarded as uncertain. He was advised to rest more completely to limit his activity according to symptoms, to eat a light reducing diet, to take phenobarbital three times daily and nitroglycerin when needed. Alcohol injection of the dorsal sympathetic nerves was considered for later use as a palliative procedure.

He improved somewhat on the above régime but not sufficiently to permit him reasonable activity or the resumption of his practice. In June, 1934, he returned for further observation. At this time he was still nervous and impatient to have something more radical done. There had been essentially no change in his physical condition from that previously recorded. The pulse was regular at a rate of 72, the heart showed only slight enlargement, the heart sounds were excellent, there was no edema, and the blood pressure was 125 systolic and 80 diastolic. The basal metabolic rate on three occasions was found to be -11, -15, and -13 per cent respectively.

With the improvement in symptoms the possibility of coronary thrombosis seemed less likely. Therefore, in spite of his age and a rather low metabolic rate, total thyroidectomy was done on June 19, 1934, with the hope of improving the coronary circulation sufficiently for his needs of light activity. He withstood the operation well and went home on the eighth postoperative day.

Two months following the operation he reported that he had had no angina pectoris and was feeling well. The basal metabolic rates at one and two months after operation were -31 and -37 per cent respectively. He looked well except for slight puffiness beneath the eyes. The heart sounds were good, and the blood pressure was 110 systolic and 70 diastolic. He had gained weight. The electrocardiogram showed no change except for slightly lower T waves. At this time he was permitted to resume light work and was given thyroid extract,  $\frac{1}{4}$  grain daily.

His condition has remained satisfactory up to the present time (December, 1935), especially when compared to the relative invalidism he suffered before thyroidectomy was done. He is well except for some coldness of his extremities and a little substernal aching on much walking, or on smoking which he has resumed. He has varied the dose of thyroid extract from  $\frac{1}{4}$  to 1 grain daily. At the higher dosages the metabolic rate is correspondingly higher and substernal oppression is more easily provoked. For more than a year now he has worked steadily in his office and has made unhurried home visits, except for three weeks vacation during the summer of 1935.

The total time elapsed since total thyroidectomy was done has been seventeen months.

**Discussion**—In 1927 a patient with heart disease and supposed thyrotoxicosis had a subtotal thyroidectomy performed at the Peter Bent Brigham Hospital in Boston and was much improved insofar as the heart condition was concerned for a period after the operation. Histological examination of the thyroid gland of this patient showed no disease. This was the experience behind the idea of thyroidectomy for heart disease. But several years elapsed before this method of treatment was actually instituted by Blumgart and Levine. At first the results were disappointing, the beneficial effects lasting but a brief time. It was then realized that total thyroidectomy, and not subtotal, was essential for the sufficient permanent reduction of the basal metabolic rate and work

of the heart, whereby the heart might recover from its state of fatigue and failure or from its coronary insufficiency. With the help of their surgical associate, Dr Berlin, Blumgart and Levine then carried out total ablation of the thyroid gland in a series of patients with obstinate angina pectoris or congestive heart failure.<sup>1</sup> In some of these patients there was a striking measure of relief, in others slight benefit, and in still others it was evident that the operation had not been advisable.

Total thyroidectomy in the treatment of obstinate angina pectoris or of recurrent congestive failure has hardly passed through its preliminary experimental phase. Some years more are needed for a completely satisfactory evaluation, but there are, at least, occasional cases still alive today who have been unquestionably benefited. One such case is that recounted above.

The selection of cases for the operation is of prime importance. In the first place the patient should have the full benefit of extensive medical treatment over a period of at least several months before being offered this operative measure. On a number of occasions we have seen patients who had had unsatisfactory response to rest and medication during the course of a few weeks, but who gradually improved with striking degree in the course of the next few months from medical therapy alone. In the second place there are patients in whom the operation is contraindicated. These include cases who are seriously ill with intractable congestive failure or recent coronary thrombosis, or, indeed, angina pectoris decubitus of very high degree. Other contraindications are cardiovascular syphilis, very low metabolic rates (minus 15 or minus 20 per cent or less), very old age (over 70), and the presence of a considerable amount of renal or pulmonary disease. It is also to be distinctly understood that total thyroidectomy does not have any beneficial effect on hypertension or on psychoneurosis which may complicate heart disease and exaggerate its symptoms. This leaves a small group of patients who are suitable for this therapeutic measure, mostly middle aged persons with angina pectoris or congestive failure, completely or almost completely free from symptoms while at rest in bed, but in whom the symptoms recur when up and about.

Total thyroidectomy itself is a major operation demanding very careful preoperative preparation, skilled surgery by an experienced operator, and careful postoperative attention. However, thyroid surgery had developed to such a degree, including its application to seriously ill thyrotoxic cardiac patients, especially by Drs Lahey and Hamilton, that the stage was already set for this new procedure of total thyroidectomy in the treatment of heart disease. Postoperatively the basal metabolic rate sinks in the course of a few months to a low level, and signs and symptoms of myxedema then begin. At such a time or just before it, say two months after operation, thyroid extract in small dosage, usually  $\frac{1}{4}$  to  $\frac{1}{2}$  grains of Armour's Extract daily, should be instituted to prevent the development of frank myxedema. Moderate hypothyroidism with a basal metabolic rate between minus 20 and minus 30 per cent is, in most cases, the desired effect. It is important for patients to be closely followed and impressed with the need of maintaining this state in which both cardiac symptoms and myxedema are held in abeyance. It seems almost certain that in some cases, at least, life can be not only considerably prolonged, but also made more comfortable by total thyroidectomy. As a radical therapeutic measure, however, it needs to be reserved as therapy of last resort and applied to perhaps 1 or 2 per cent of cases with angina pectoris or congestive failure.

#### CHRONIC CONSTRICTIVE PERICARDITIS

Case V—B K, a girl aged ten years, entered the hospital on October 13, 1931, with a history of having lived a semi-invalid life since the age of five and one-half years due to a markedly enlarged abdomen resulting from the presence of much ascitic fluid. When she was twenty months old she suffered from what was apparently an attack of acute pericarditis, and her abdomen became enlarged at that time. At the age of two and one-half years a laparotomy was performed and a gangrenous appendix was removed. No tubercles were seen on the peritoneum at the time of operation. A drain was inserted, and the patient made a good recovery. The fluid returned in about three weeks but following an abdominal tap one month later there was no recurrence of fluid for three years. At the age of five and one-half years the abdominal fluid returned, and six months later a Talma operation (omentopexy) was done. Abdominal fluid injected into a guinea-pig gave negative results. There was no improvement following this operation, and at the age of nine the patient entered a second hospital for further study. Her abdomen was tapped at that time, but not again after that until her entrance into the Massachusetts General Hospital in the fall of 1931 when 6240 cc of straw-colored fluid with a specific gravity of 1.013 were removed.

Her mother had died of tuberculosis during the patient's infancy Her father is living and well

Physical examination showed a thin somewhat pale, young girl with heart apparently normal in size and sounds and without murmurs, and with prominent jugular veins and a large protuberant nontender abdomen filled with fluid (Fig 167)  $\times$  Ray examination showed the heart and great vessels somewhat displaced to the right and anchored to the diaphragm, no pulsation was evident at the right border of the heart and great vessel shadow, the right pleura was thickened

The electrocardiogram showed normal rhythm rate 100, with inverted T waves in Lead 2 (Fig 169 A)

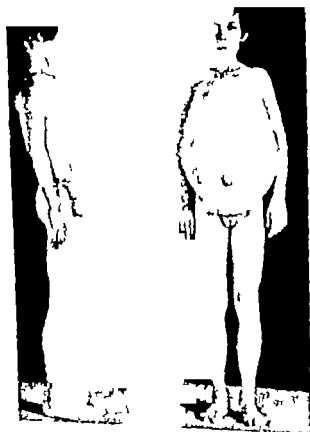


Fig 167—Case V at the time of her disability Her condition was unchanged for seven years (five to twelve years of age)

Advice was given at that time that the chest be explored surgically and the adhesions constricting the right auricle, right ventricle and great veins be freed.

After an interval of two years this girl returned to the hospital in an unchanged condition with persistence of the enlargement of the abdomen. The serum protein measured 4.3 per cent.  $\times$  Ray and electrocardiographic findings were as before.

Pericardial resection was carried out on November 16, 1933 and a moderately thickened pericardium containing calcareous plaques was removed from over the right ventricle and right auricle by Dr Churchill. The pericardial tissue that was removed showed fibrosis and calcification on examination There was a stormy time for two days after the operation. Finally spon

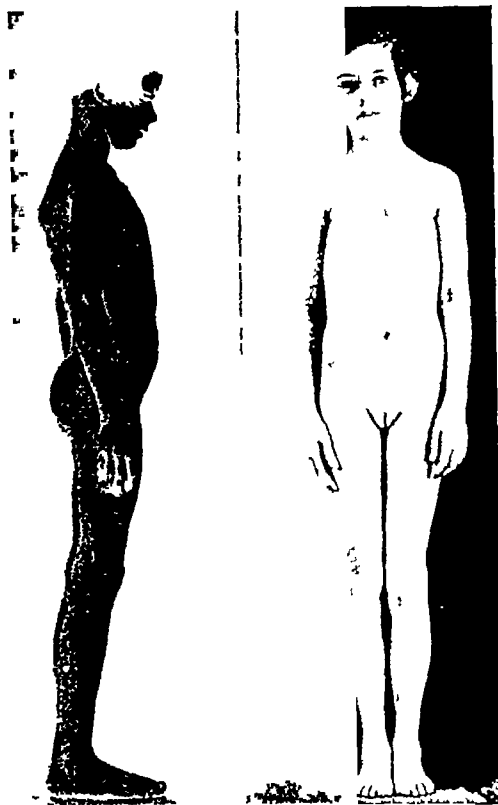


Fig 168—Case V one year and a half after operation Her cure was completely effected within a few months of the pericardial resection

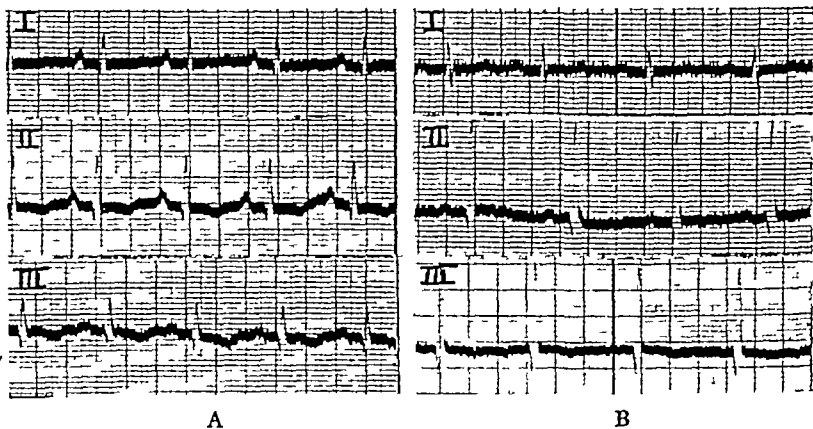


Fig 169—Case V

taneous diuresis began and in the course of a few months the ascites completely disappeared. She has been in excellent health since and looked well when she was last examined by us on May 16 1935 (Fig 168)

The electrocardiogram on May 16 1935 showed normal rhythm at a heart rate of 80, with slightly upright T waves in Lead 1 flat T waves in Lead 2, and very slightly inverted T waves in Lead 3 this record differed from that taken before the operation in that the T waves were more normal and the voltage of the QRS waves was greater (Fig 169, B)

**Discussion.**—Chronic constrictive pericarditis or Pick's disease, recognized by only a few medical observers over a period of several hundred years prior to the last decade, is at last amenable to treatment. Formerly a hopeless disease treated by palliative measures to relieve dropsy, consisting chiefly of rest, restriction of fluid and salt intake, abdominal paracentesis and diuretics, it now yields to surgery in a considerable percentage of cases

In 1895 Delorme of Paris tried to persuade the surgeons of his hospital to undertake to free the heart from its constricting pericardial adhesions. After three years of failure in his attempt to interest them, Delorme,<sup>6</sup> in 1898, announced his ideas to the medical world in an open meeting in Paris, several years before Brauer<sup>7</sup> offered his much less important plan of freeing the heart (rib resection and cutting of external adhesions). It is strange that Brauer's operation became much better known than the more vital pericardial resection advocated by Delorme. Finally, in 1913, Sauerbruch and Rehn independently carried out Delorme's suggestion. During the next ten years a few cases were operated upon in Germany, but it has been only in the last decade that pericardial resection has been firmly established as a cure for chronic constrictive pericarditis.

It is important in the first place to establish the diagnosis of chronic constrictive pericarditis. Following an infection which is often obscure but involves the pericardium and at times the pleurae and peritoneum (polyserositis), the pericardium becomes thickened, callous, constricted, and sometimes calcified. The cause of the original acute pericarditis is often unknown. In a few cases it is definitely tuberculous, in others it is associated with pneumonia and pleuritis, in a few it is septic in nature (when there is survival), but it seems never to be rheumatic. As noted by one of us in a recent



paper<sup>10</sup> on chronic constrictive pericarditis, "The leading clues are the result of inflow stasis, namely, (1) the insidious onset of dropsy in a young person, (2) preponderant liver enlargement and ascites, (3) increased prominence of the jugular veins, (4) normal or relatively normal heart in the presence of dropsy without nephritis, and (5) low blood and pulse pressure and paradoxical pulse. Other important clues are (6) x-ray evidence (poor pulsation, calcification, chronic pleuritis), (7) electrocardiographic abnormalities (low voltage or coronary T waves in chronic disease in early youth), and (8) previous history of acute pericarditis or polyserositis." The three conditions most commonly confused with chronic constrictive pericarditis are rheumatic heart disease with mitral stenosis and congestive failure, primary cirrhosis of the liver, and polyserositis including instances of perihepatitis or frosted liver.

The operation itself, done under general anesthesia, preferably ether, is a difficult one and to be trusted only to a skilled thoracic surgeon. About an hour is needed for the approach to the chief operative field, namely, the pericardium itself. Three or four rib ends and costal cartilages, usually the fourth, fifth and sixth, and the left edge of the sternum are removed. The pleurae are carefully retracted, the pericardium incised and both parietal and visceral layers, usually adherent to each other and as thick as shoe leather, are carefully dissected off from the surface of the heart, most commonly from the right ventricle and right auricle. This procedure takes about another hour, and, if successful, the heart obviously expands during the course of the operation while it is being freed from the constricting pericardium, the pulse improves and the pulse pressure increases. Recovery may be rapid or slow following the operation. Sometimes a spontaneous diuresis develops during the course of the very first week postoperatively and in two or three weeks the congestion may entirely disappear, resulting in an early cure. In other cases progress is much slower and several months may elapse before there is marked improvement or cure. In a few cases operation may be unsuccessful and in another few it may cause an early fatality. In our own series of 12 cases of pericardial resection done at the Massachusetts General Hospital by one surgeon (Dr. E. D.

Churchill) there have been six cures, two other recent cases apparently on the way to a cure or high degree of improvement, and one other case more than 50 per cent improved. Thus, although this disease is rather rare, it is now of vital importance that it be recognized and its victims offered this new opportunity for cure. The history recounted above is one of our successful cases.

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### RECENT ADVANCES IN THE TREATMENT OF ARTERIAL HYPERTENSION

#### SYNOPSIS

##### I. General Consideration of Therapeutic Measures

##### II. Chemical Substances

- The nitrites.
- The alkyl nitrates.
- Bismuth subnitrate
- Tissue extracts.
- Histamine.
- Acetylcholine.
- Acetyl- $\beta$  methylcholine
- Adenosine and adenylic acid
- Cucurbitacin
- Potassium thiocyanate.
- Ovarian hormones

##### III. Dietary Measures.

##### IV. Surgical Measures

- Procedures to influence the hormonal production of the glands of internal secretion
- Section of the splanchnic nerves.
- Direct denervation of the suprarenal glands.
- Suprarenalectomy
- Operations for the purpose of influencing nerve impulses of the vasomotor system
- Denervation of the kidneys.
- Section of the splanchnic nerves.
- Spinal nerve root resections.
- Combined surgical measures.
- Critique of the surgical treatment of arterial hypertension

##### V. Conclusions

##### VI. Bibliography

DEVIATIONS from the normal level of arterial pressure are often responsible for clinical symptoms and frequently lead to disturbances of bodily functions. While the prognosis in arterial hypotension is good as far as structural disturbances and longevity are concerned, the serious cardiac, neurologic, renal and other organic complications of chronic arterial hypertension are well recognized. In the prevention of these secondary vascular disturbances and "organ insufficiencies," adequate treatment of "uncomplicated" hypertension is essential. The following discussion will be restricted to an evaluation of attempts recently undertaken for the treatment of "uncomplicated" arterial hypertension.

### I GENERAL CONSIDERATION OF THERAPEUTIC MEASURES

Efforts to abolish arterial hypertension effectively have so far been uniformly characterized by failure. This is not surprising when one considers that in spite of significant evidence indicating that hypertension is the result of mechanisms of varied etiology, the details of these mechanisms are little understood<sup>1</sup>. As a result, no successful therapy directed against etiologic factors exists, nor can it be rationally devised at present. All one can attempt to do is to search for measures which tend to reestablish the normal level of the arterial pressure with the maintenance of adequate capillary blood flow through the tissues both at rest and during physiologic activities of the body. This latter consideration is particularly important, for although one can lower the blood pressure with relative ease in a number of ways, there is usually ultimate damage to the organs.

There are a number of facts now firmly established, the knowledge and proper evaluation of which are essential in the effective treatment of hypertension. In the majority of instances of arterial hypertension, in which both the systolic and the diastolic pressures are considerably elevated and the pulse pressure is usually high, the primary and most significant change consists in an increase in the "tonus" of the arteriolar as well as of the arterial walls<sup>2, 3</sup>. The relative degree of involvement of the arteriolar and arterial systems, respectively, varies in different types of hypertension. The chief factor is usually the increased tonus of the arteriolar rather than of the

arterial system, which in turn causes a notable increase in the resistance of the vascular tree to the blood flow. The pressure within the capillaries, as judged from the behavior of the cutaneous capillaries and of the spinal fluid pressure, is usually but not necessarily, normal. Similarly, the systemic venous pressure and the pressure relations within the pulmonary circuit are, in the majority of uncomplicated cases, within the limits of normal. The circulating blood volume and the viscosity of the blood are also normal. Since the cardiac output, the stroke volume of the heart, and the maximal and mean velocities of the circulation are likewise normal, it follows that the mean supply of blood to the tissues is the same in patients with hypertension as it is in normal subjects.<sup>3 4 5</sup> These findings, now confirmed, clearly indicate also that the increase in arteriolar resistance is diffuse throughout the body. That such is actually the state of affairs in the skin and in the striated muscle tissues is shown by direct observations recently made in this laboratory.<sup>6 7</sup> That in some of the organs ischemia and hyperemia may exist simultaneously as a result of a relatively increased constriction or relaxation of the arterioles is possible, and from certain observations is even probable.<sup>8</sup> This does not, however, alter the fundamental fact that in spite of change in the physical properties (changes in tonus) of the arterioles and of the arteries a remarkable homeostatic regulation exists in hypertension which results in an adequate and normal supply of blood to the tissues at rest and under physiologic stimuli. This homeostatic adjustment is accomplished by increased work on the part of the heart and by increased arterial and arteriolar pressure on the part of the circulation. It is important to reemphasize that the circulatory adjustments in hypertension are performed with good economy, and that *there is no overabundance of blood supply to the organs in hypertension*. Such considerations inevitably lead to the conclusion that *arterial hypertension is primarily a progressive obstructive disease of the arteriolar system and a progressive alteration of certain physical properties of the arterial system*. The elevations of the diastolic and systolic pressures are secondary manifestations, and they must be looked upon as compensatory adjustments for the maintenance of adequate capillary circulation in the tissues.

The exact *nature of the change* in the arterioles and arteries is unknown. At the present time all that we know is that the increase in "tonus" can be either reversible, or partially or completely fixed. It has been assumed from indirect clinical evidence that the source of the increased tonus, particularly in the early stage of hypertension, is increased efferent sympathetic nervous impulses in the vasomotor system. Actually, clinical experimental attempts to demonstrate such striking difference in the tonus of the autonomic nervous system in patients with arterial hypertension as compared with that in control subjects have thus far failed<sup>7, 9</sup>. Practically all the increased vascular responses observed in hypertension, which have been claimed to result from increased sympathetic impulses, can be explained as due to increased irritability of the vessels themselves. Our knowledge is therefore in a paradoxical state, namely, in spite of the fact that we can demonstrate changes in the tonus of the arterioles and arteries, we cannot demonstrate the increased sympathetic impulses, nor can we identify circulating chemical substances leading to increased tonus<sup>10</sup>.

This consideration of the mechanism of arterial hypertension is helpful in defining those characteristics which therapeutic measures must possess in order to be beneficial in hypertension. An effective measure must obviously decrease arteriolar and arterial tonus and resistance without essentially disturbing other fundamental characteristics of the circulation, such as the cardiac output, the velocity of blood flow or the volume of circulating blood. The measure must maintain normal and adequate blood flow to the organs, particularly to the heart, brain and kidneys, at rest and in times of physiologic stress. The effect of the measure must be such that sudden drops in the blood pressure are avoided, and if possible the spontaneous fluctuations present in hypertension toned down. Establishment of a permanent lower level should occur gradually. The vasomotor responses essential to normal bodily functions should not be affected.

Let us ascertain whether the measures introduced fulfill the rationale of these requirements.

## II. CHEMICAL SUBSTANCES

**The Nitrites**—The vasodilator properties of this group of substances have been known for a long time. It is only in late years, however, that the rationale of their use in arterial hypertension and in angiospastic disorders has been examined critically. Recently it has even been claimed that minute amounts of nitrites are normal constituents of the human blood<sup>11</sup>. The nitrites act chiefly, if not entirely, on the peripheral vascular system and produce vasodilatation, probably as the result of direct action on the smooth muscles of the vessel walls. The site of their activity is chiefly the arterial side of the vascular bed. The depressor effect is greater on the systolic than on the diastolic pressure. The comparative stability of the diastolic pressure suggests that the dilator effect of the nitrites on the small arteries and arterioles is neither constant nor marked. As far as the cardiac output is concerned, it either remains normal or becomes reduced. Similarly, the kidney function remains unaltered or becomes reduced as the result of the changes in the cardiovascular system<sup>12</sup>. These changes suggest that in some respects the nitrites are suitable agents for reducing arterial pressure. Their greatest drawback is their fleeting action. Moreover, in effective doses they may temporarily impair kidney function, and with the patient in the erect position they may cause increased strain on the circulation and at times fainting. The effects of sodium nitrite last but one or two hours, and some of the related compounds, such as amyl nitrite, have an action of much shorter duration, which can be measured in terms of minutes. Recently attempts have been made to use compounds that are absorbed slowly from the gastro-intestinal canal, such as bis-muth subnitrite, in order to insure a longer persistence of action. So far, however, such efforts have not proved successful. The short duration of action of the nitrites results in a constant and abrupt fluctuation of the arterial pressure, which in turn precipitates symptoms, and therefore their continued use may even become dangerous, particularly in patients with arteriosclerotic changes. In view of these considerations, the main use of the nitrites is in acute vasospastic states, such as occur in vascular crises.

**The Alkyl Nitrates**—The principal representatives of



this group, glycerol trinitrate, erythrol tetranitrate and mannitol hexanitrate, can induce marked reduction in the arterial tonus, particularly if the latter is increased. The duration of effect of this group of substances is again relatively short, though erythrol tetranitrate may lower the blood pressure for from two to three hours, and mannitol hexanitrate for as long as four or five hours. As far as the maximum depression of the blood pressure is concerned, 1 mg ( $\frac{1}{60}$  grain) of glycerol trinitrate is equivalent to about 30 mg ( $\frac{1}{2}$  grain) of erythrol tetranitrate or to 60 mg (1 grain) of mannitol hexanitrate by mouth. It takes from twenty to thirty minutes for the last two substances to exert their action after oral administration.

For the same reasons as apply to the nitrites, the routine use of alkyl nitrates in arterial hypertension is not feasible, furthermore they are too expensive. Their main indication is in acute vasopastic states, such as occur in vascular crises and in angina pectoris.

**Bismuth Subnitrate**—The beneficial effect of this substance has been reported by Stieglitz<sup>13</sup>. It has been claimed that mild relaxation of the arterial system follows the oral administration of doses of 0.6 Gm (10 grains) three times daily. Since this salt is relatively insoluble, there is a continuous liberation of minute amounts of nitrate within the intestines. It is claimed that under the influence of the colon bacillus the liberated nitrate ions are reduced to nitrites. Stieglitz and Palmer offered evidence to show that following the administration of bismuth subnitrate the nitrite concentration of the blood increases<sup>14</sup>. Such medication serves a double purpose, according to Stieglitz. It reduces the arterial pressure and relaxes the arterioles, thereby breaking "the vicious circle of arteriolar fatigue". According to the experience of Stieglitz, a demonstrable reduction in the arterial pressure occurred in 77 per cent of the patients<sup>13</sup>. The maximal reduction may be reached only after weeks of using the drug. Since the medication is certainly harmless and at the same time is inexpensive, it deserves trial as a symptomatic remedy, although in routine clinical use one has difficulty in seeing its benefit. Several reports in the literature also deny its therapeutic value.

**Tissue Extracts**—During the past few years renewed claims have been made that extracts of muscle, liver, heart,

pancreas, brain, kidney and spleen exert a beneficial influence in arterial hypertension and in other vascular disorders, particularly angina pectoris. Such extracts, under the trade names of "myol," "lacarnol," "myoston," "padutin," "hormon kardiol" and others, are extensively used in Europe and America. That tissue extracts can reduce the arterial pressure in experimental animals has been known for a long time. The active factors were thought to be vasodilator substances. The recent claim, however, is that the alleged beneficial effect of these substances depends on circulatory hormones and only secondarily on vasodilator substances. For the existence and the nature of such circulatory hormones little and rather poor evidence is found in the literature, it is questionable, therefore, whether any greater benefit can be attributed to these preparations than to the combination of vasodilator substances contained in tissue extracts. These substances include histamine, choline and adenosine or adenylic acid and their derivatives. The cardiovascular effect of other substances present in tissues is negligible. Until we attain greater understanding of the effect of these substances on the vascular system, the clinical application of tissue extracts containing variable concentrations of vasodilator substances must be considered as empirical and unsettled.

**Histamine** is often considered as a potent vasodilator substance, and in certain species of animals, under experimental conditions, such is the case. It has been shown, however, that normal subjects given an intravenous infusion of histamine up to toxic doses continuously for two hours fail to respond with an appreciable lowering of the arterial blood pressure<sup>15</sup>. In some instances the diastolic pressure shows a tendency to fall, but in numerous instances it remains unaltered. As judged from the behavior of the hemodynamics and from the vascular responses, arteriolar dilatation develops only in certain organs, and is associated with such changes in the heart and other organs as to make the therapeutic application of this or related substances as vasodilators questionable. It is of especial interest that when observations similar to those conducted on normal subjects were made on a group of patients with arterial hypertension, the response was similar in every respect to that observed in normal subjects. From the same concen-

tration of histamine the degree of elevation of the skin temperature was the same in normal subjects as in patients with arterial hypertension. This indicates that the degree of relaxation of the cutaneous arterioles was actually less in the hypertensive than in the normal subjects, but that the degree of increase in blood flow was the same in both groups<sup>16</sup>. This constitutes additional evidence that in arterial hypertension the arteriolar responses to physiologic and other stimuli are such that the resulting blood flow is within the limits of normal.

These findings, together with its fleeting action and the fact that it is entirely ineffective even in massive oral doses, make histamine entirely unsuited for use in the treatment of arterial hypertension.

**Acetylcholine**—The work of Dale and his associates<sup>17</sup> has amply demonstrated that choline, a derivative of lecithin, and its esters represent the most potent vasodilator constituents of tissue extracts. Recently it has also been claimed that some of the choline compounds play an important rôle as chemical mediators of nerve impulses on cells with motor activities. It has also been proposed that choline acts as a regulator of intestinal peristalsis and tone. It is a remarkable pharmacologic fact that by the introduction of an acetyl radical the physiologic potency of choline in reducing arterial pressure increases one hundred thousand times, and such a minute amount as 1 cc of a 1:100,000,000 dilution of acetylcholine produces a fall in the blood pressure of the rabbit of 20 to 25 mm Hg. It was natural, therefore, to expect that a substance with such biologic properties might be a suitable agent for the treatment of arterial hypertension. As a result of such claims by French clinicians, acetylcholine (under the trade name of "acecoline") came into use as a vasodilator.

The following consideration of the action of acetylcholine in man reveals at once that its therapeutic applicability as a vasodilator is limited. First of all, it has been demonstrated that man is relatively tolerant to this substance<sup>18</sup>. After oral administration of even massive doses no systemic effects are noted. Even when as large a dose as 1 Gm (15 grains) is infused evenly intravenously within a period of ten minutes, and mild toxic manifestations are precipitated, the arterial pressure either remains normal or is only slightly reduced. A

moderate degree of arteriolar dilatation develops, but circulatory adjustments apparently compensate for the dilatation in such a manner that the blood pressure does not change significantly. Furthermore, the effect is only transient, owing to the fact that acetylcholine is promptly destroyed within the blood stream. The effect of intramuscular administration of acetylcholine is unreliable and variable. In the few instances in which we have observed the effect of acetylcholine in patients with arterial hypertension we have found the response of the cardiovascular system similar in every respect to that in normal subjects.

These considerations, together with the expense, clearly demonstrate that acetylcholine is not a suitable substance for routine use in arterial hypertension. In certain acute vasospastic states, on the other hand, it may be useful when it is administered intravenously with proper understanding of its pharmacologic and toxicologic qualities.

**Acetyl  $\beta$  Methylcholine**—This substance, like acetylcholine, produces vasodilatation and a certain type of parasympathetic stimulation.<sup>19</sup> When given intravenously to anesthetized animals, the vasodilator effect of the two compounds is of the same order of magnitude, but the action of acetyl  $\beta$ -methylcholine ("mecholin") is of longer duration owing, presumably, to its slower hydrolysis in the blood. Following subcutaneous injection, acetyl  $\beta$  methylcholine is more effective than acetylcholine. The general as well as the cardiovascular responses in normal human subjects following the continuous intravenous infusion of acetylcholine and acetyl  $\beta$  methylcholine are similar, but the latter substance is approximately two hundred times as potent as the former.<sup>20</sup> The duration of action of these compounds is very short. In man, mild systemic responses can be induced following oral administration of acetyl  $\beta$  methylcholine. These facts indicate that for parasympathetic stimulation and in acute vasospastic states acetyl  $\beta$  methylcholine offers advantages over acetylcholine. The effective subcutaneous or intramuscular dose varies from one individual to another, and may be from 5 to 30 mg ( $\frac{1}{12}$  to  $\frac{1}{2}$  grain).

**Adenosine and Adenylic Acid.**—These and related compounds are, like histamine and choline, natural constituents of

the human body and active principles of organ extracts Adenosine is formed with ease by the hydrolysis of nucleic acid Adenosine and adenylic acid are practically identical in their pharmacologic effects, which depend on the ease with which they are deaminized in the body<sup>21</sup> They act primarily on the heart, and, to a lesser extent, as dilators, on the vessels, including the coronary arteries Effective doses produce slowing of the heart and disturbances in the intracardiac conduction, leading to block In tachycardias, including auricular fibrillation, they may induce slowing In man, intravenous injection of 0.2 to 3 cc. of a watery solution causes sweating, a sensation of warmth, tremor, and restlessness associated at first with tachycardia and later with bradycardia<sup>22</sup> The T waves of the electrocardiogram may become flat, and delay in conduction may develop

The evidence for the beneficial effect of these compounds in disease is meager The combined effect of the cardiac slowing, disturbances of cardiac conduction, vasodilatation and fall in blood pressure which they produce is such that the function of the heart and the state of the circulation are usually not improved, and at times are even made worse In view of this fact and also in view of the fact that their action is only transient, the therapeutic use of these compounds is undesirable

The pharmacologic and therapeutic effects of histamine, choline, and adenosine and its related compounds cast *serious doubt on the claims as to the benefit of tissue extracts in hypertension* and in certain other vascular disorders At best they produce only a fleeting effect, and when administered orally they must be practically inert

**Cucurbocitrin**—Extracts of watermelon seed contain glucosides and saponins, which, according to Barksdale, produce a lowering of the arterial pressure as a result of peripheral dilatation<sup>23</sup> It is claimed that this depressor effect is also obtained after oral administration No ill effects have been observed This compound, under the name of "citrin," has so far not proved a particularly useful agent No further report on its therapeutic use has appeared recently

**Potassium Thiocyanate**—Ever since Pauli's claim in 1903 that thiocyanate was effective in reducing high blood pressure, the use of this drug has been advocated from time to

time Its toxic properties have not been sufficiently appreciated, however, in spite of the fact that they were emphasized by Claude Bernard in 1857 The therapeutic dose should not exceed 1 Gm (15 grains) per day, and even after such a dose toxic reactions may occur After larger doses, muscular weakness, psychosis, dermatitis, cardiac pain and fatalities occur Impaired renal function apparently increases toxicity Some persons show susceptibility to the drug The margin of safety between the blood pressure reducing and the toxic doses is narrow The detailed mechanism of its action has not been investigated as yet As judged from recent reports, the indiscriminate use of thiocyanate is dangerous

**Ovarian Hormones**—It is claimed, especially by German writers, that certain extracts of the ovarian hormones, particularly follicular hormones, lower the pressure and alleviate the symptoms in hypertension That progynon, administered orally in doses of 1800 units daily, is capable of abolishing the hot flashes of menopause is known This is the more interesting because, in spite of the fact that in menopause there is underproduction of estrin and overproduction of prolan A, the hot flashes cannot be directly related to the low estrin content or to the high prolan A production<sup>24</sup> We have pointed out before that the symptoms of uncomplicated menopause, of hypertension appearing during menopause, and of uncomplicated hypertension are essentially identical<sup>25</sup> Hence estrin may well exert a beneficial effect on the symptoms of hypertension Whether such therapy influences the level of the arterial pressure has not been established In 2 cases followed by Albright such hypertension remained unchanged<sup>26</sup>

### III. DIETARY MEASURES

In recent years the most important advance in the dietary treatment of high blood pressure consists in the correction of dietary restrictions and fads advocated in the past There now exists adequate evidence that primary hypertension is not associated with metabolic disturbances, and that the kidney function remains good or fair in the majority of instances In the Boston City Hospital about 10 per cent of the cases with nephrosclerosis die from uremia It is doubtful whether in

this 10 per cent early protein or salt restriction would essentially have altered the outcome. Hence low protein and intensely restricted salt diets have been abandoned. In view of the chronicity of the condition, such diets often result in deficiency states and precipitate secondary complications. The only significant fact related to diet which we have learned is that in cases of overweight a balanced low caloric diet, which will result in weight reduction, will also result in effective and permanent lowering of the blood pressure. Reduced weight, in addition, lessens the work of the heart. Thyroid extract, dinitrophenol or other reducing agents should not be used, for they may precipitate cardiac disturbances. It is obvious that condiments and an excess of salt should be avoided. It is perhaps rational to encourage a moderately increased water intake, but no reliable evidence has yet been furnished that natural or artificial mineral waters have any specific beneficial effect. Alcohol in minute amounts is a natural compound of the body and burns with ease. Its excessive use is especially harmful to hypertensive patients, its moderate use, particularly in the form of beer or wine, is actually beneficial as a mild relaxer, sedative and vasodilator. In acute vasospastic states it has a distinctly beneficial effect.

#### IV SURGICAL MEASURES

In recent years vigorous attempts have been made to influence hypertension permanently through surgical measures. In view of the fact that the primary disturbance in arterial hypertension consists in reversible alterations in the physical properties of the arteriolar and arterial systems, and in view also of the fact that during the past decade neurosurgery has made important contributions in the treatment of certain peripheral vascular disorders, it is natural that such attempts should be made. On the other hand, it is particularly important that physicians should realize that the value of these measures is far from being established, and that they must be considered as empirical rather than as based on a rational knowledge of the etiology or, for that matter, even of the mechanism of hypertension.

The surgical measures which have been advocated may be divided into two main groups (a) procedures devised to

influence the hormonal production of the glands of internal secretion, and (b) operations for the purpose of influencing nerve impulses of the vasomotor system

#### PROCEDURES TO INFLUENCE THE HORMONAL PRODUCTION OF THE GLANDS OF INTERNAL SECRETION

Of the glands of internal secretion the pituitary, thyroid, adrenal and ovarian glands have been regarded as being responsible for the development of arterial hypertension. There is little basis for such claims, the most tangible evidence so far presented being the claim of Cushing<sup>27</sup> and others that *basophilic adenoma or basophilic infiltration of the anterior lobe of the pituitary* is associated with hypertension. The significance of basophilic infiltration of pituitary cells in relation to hypertension, however, is not settled, and we lack adequate controls. Thus recently Ahlström<sup>28</sup> has denied the existence of a direct relationship between basophilic infiltration and hypertension. Patients with hypertension frequently have no basophilic infiltration and, contrariwise, patients with basophilic infiltration may have normal blood pressure. He quotes Spark, who also failed to find a relationship between basophilism and hypertension\*. So far, perhaps fortunately, nobody has devised surgical procedures to influence pituitary secretion as a measure in the treatment of arterial hypertension. Reports on attempts to irradiate the pituitary gland with x rays are beginning to appear in the literature, but no convincing evidence as to the benefit of this procedure has yet been presented. Moreover, it is not clear whether such a measure is harmless.

There are two arguments that may be brought forward in favor of the *suprarenal origin of hypertension* (1) that an overproduction of adrenalin is responsible for hypertension, (2) that an unusual sensitivity to a normal secretion of the gland exists. With the exception of the rare cases of medullary tumors of the adrenal associated with the paroxysmal type of hypertension, there is no direct or indirect evidence

\* Since this paper was sent in for publication a report by Scriba has appeared (*Die basophilen Zellen des Hypophysenhinterlappens und ihre Beziehungen zum Hochdruck und zur Eklampsie Klin Wchnschr* 14 1589 1935). He also failed to find a causal relationship between basophilic infiltration and hypertension.



supporting the contention that circulating adrenalin is responsible for arterial hypertension *The hemodynamics and behavior of the patient with arterial hypertension differ essentially from those observed in animals or in man during experimentally induced hyperadrenalism* We have observed that histamine, which in several respects is an antagonist of adrenalin, exerts no influence on any type of hypertension It is also significant in this connection that complete ablation of the thyroid gland apparently fails to influence the course of arterial hypertension It is well known that thyroid secretion exerts a sensitizing effect on the action of adrenalin on the cardiovascular system One would therefore expect that if hyperadrenalinemia, or increased sensitivity of the blood vessels to normal adrenalinemia existed, a change in the hypertension would follow the complete elimination of thyroid secretion

In spite of these basic considerations, surgical attempts to influence suprarenal secretion have been made and beneficial results have been claimed Three types of operation have been performed for this purpose (1) unilateral or bilateral section of the splanchnic nerves, (2) direct denervation of the suprarenal glands, (3) various degrees of suprarenalectomy

**Section of the Splanchnic Nerves**—This operation was suggested as a therapeutic procedure in arterial hypertension by Danielopolu as early as 1923 In 1923 Pende<sup>29</sup> advised section of the left splanchnic nerves for the production of vasodilatation within a large abdominal area and for the inhibition of adrenal secretion Pieri<sup>30</sup> in 1932 resected both splanchnic nerves in 5 cases of essential hypertension Craig and Brown<sup>31</sup> performed unilateral or bilateral resection of the splanchnic nerves and removed the first lumbar ganglion in 5 cases They claimed that the operation is relatively safe In only one of their patients was the subjective and objective improvement striking, in two the only change was the reduction in the pressure reactions to cold, and in the remaining two with early renal involvement and advanced organic changes in the arterioles no benefit was noted Craig and Brown recognize the fact that removal of the sympathetic nerves does not materially alter the arterial pressure They think that resections influence the "response" or vasopressor reactions in hypertension Excessive reactions, it is claimed, cause abnormal

wear and tear on the vascular system. The purpose of the surgical measure is to block or modify these excessive responses before the onset of organic or irreversible lesions. Patients with the "spastic" or "vasomotor" types of hypertension are therefore the most suitable subjects for operation. In a recent communication to me<sup>22</sup> Dr. Brown states that in his opinion, however, the results with subdiaphragmatic bilateral resection are "rather equivocal and not at all dramatic."

Peet<sup>23</sup> has performed bilateral splanchnic nerve section on over 60 patients, all of whom had a systolic blood pressure of 200 or over. His intention was (1) to diminish peripheral blood volume through splanchnic dilatation, (2) to diminish adrenal secretion, and (3) to abolish abnormal vasoconstrictor effects of kidney origin, provided sclerotic changes in the kidney were not too advanced. He also claims that it is conceivable that after removing the elements of spasm and the strain of hypertension, the vessels "might" return to normal. He believes that in 6 cases in which complete relief was obtained such a process accounted for the return of normal kidney function. He confesses that no criterion as to the operability has yet been found. Marked fundus changes and evidence of greatly impaired kidney function are not contraindications. In a recent personal communication Dr. Peet<sup>24</sup> states: "We are continuing to do splanchnic operations for hypertension and believe our results are, on the whole, superior to those obtained by any other of the various surgical procedures. The operation, as developed by us, consists of a superdiaphragmatic approach with resection of the greater and lesser splanchnic nerves and of the lower dorsal sympathetic chain, including 10, 11 and 12 dorsal ganglions. We have always performed the operation bilaterally. Sixty-two per cent of our patients who have gone at least four months after operation showed very definite improvement and a considerably higher percentage have had relief of symptoms. About 15 per cent are cured so far as any evidence of hypertension is concerned. These have all gone at least six months and have maintained normal blood pressure while actively engaged in their former occupations, and have had a complete disappearance of all eye and kidney findings. We have operated over 100 patients. The longest has been followed two years and is maintaining a nor-

mal pressure, normal vision, and normal kidney findings. Before operation he had a blood pressure ranging from 240 to 280 over 180 diastolic. He had choked discs and markedly impaired renal function."

**Direct Denervation of the Suprarenal Glands**—This procedure was devised by Crile<sup>35</sup> for the relief of symptoms of neurocirculatory asthenia. Others<sup>36</sup> have observed indifferent results following the same operation. It is said that this technic is now practiced in some clinics for the relief of hypertension. Recently, Rogoff\* has reported the occurrence of "Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus." He warns "The course and outcome in this case strongly support the contention, repeatedly made by me since 1918, that surgical intervention with the adrenals for various conditions (Raynaud's disease, spontaneous gangrene, hypertension, epilepsy, gastric ulcer, thyroid disease, diabetes, and the like) is to be deprecated. The very fact that it is alleged to be of benefit in so great a variety of diseases ought to render the practice suspect."

**Suprarenalectomy**—The experiences of Galata,<sup>37</sup> of Monier-Vinard, and Desmarest<sup>38</sup> and of Pieri<sup>30</sup> with unilateral suprarenalectomy do not reveal any benefit following operation. The blood pressure became lowered for only a short period, and obviously this was the result of surgical trauma. The surgical removal of pheochromic tumors of the suprarenal, on the other hand, has resulted in marked benefit to the patient.<sup>39</sup>

DeCourcy, DeCourcy and Thuss,<sup>36</sup> believing "that the most rational method of treatment of essential hypertension is the surgical excision of sufficient amounts of glandular tissue to relieve the excessive functioning of the gland itself," removed about two-thirds of each suprarenal gland, including both medulla and cortex. They claim benefit in some of the patients as far as symptoms and lowering of the blood pressure are concerned. From their presentation it is difficult to judge the extent of the control observations.

\* Jour Amer Med Assoc, 106 279, 1936

## OPERATIONS FOR THE PURPOSE OF INFLUENCING NERVE IMPULSES OF THE VASOMOTOR SYSTEM

These procedures may be grouped into the following main groups (1) surgical denervation of the kidneys, (2) splanchnic resections, (3) anterior spinal nerve root resections, (4) combination of these procedures

**Denervation of the Kidneys**—This procedure was carried out recently by Page and Heuer<sup>40 41</sup> both in patients suffering from severe essential hypertension and in patients with chronic nephritis. Heuer freed the renal vessels and after visualizing the sympathetic nerves, removed the nerves from both the ventral and the dorsal aspects of the vessels. In the one patient suffering from severe essential hypertension, the operation failed to alter the level of the pressure or to improve the function of the kidney. In patients with nephritis the blood pressure was lowered for a few weeks after operation, but in all except 1 case it then regained its original level. The urea function of the kidney remained essentially unchanged, two of the patients exhibited increased concentrating power.

**Section of the Splanchnic Nerves**—This procedure has already been discussed in connection with denervation of the adrenals (p. 1356).

**Spinal Nerve Root Resections**—This operation, proposed by Adson and Brown,<sup>42</sup> consists in sectioning the anterior and probably also the posterior nerve roots from the sixth thoracic to the second lumbar segment. Even with such an extensive influence on vasomotor control and on intra abdominal pressure, the result was not striking. Page and Heuer<sup>43</sup> report that following this type of operation in a young girl the arterial pressure returned to normal for seven months. Dr. Brown<sup>42</sup> at present believes that in the malignant forms of hypertension the procedure has no influence on the course of the disease, but that in benign hypertension good results have been observed as late as five years after operation.

It is important to remember that in male subjects bilateral complete lumbar sympathectomy will induce sterilization. The patient will be able to perform the sexual act, with orgasm, but without ejaculation.

**Combined Surgical Measures**—Finally, attempts are being made to investigate the effect of various combinations of the methods described above. The possible value of such a procedure can be surmised from the foregoing discussion.

#### CRITIQUE OF THE SURGICAL TREATMENT OF ARTERIAL HYPERTENSION

The following points have been, or may be, proposed in favor of the surgical treatment of primary (essential) hypertension: (1) there is an increased secretion of adrenalin which is responsible for hypertension; (2) Primary hypertension develops secondarily from a primary pathology in the kidney and is precipitated through afferent nervous impulses from the kidney; (3) There is a hyperactive vasomotor center in hypertensive patients with resulting increased motor nerve impulses and exaggerated pressor responses; (4) Even if there exists no increased vasomotor tonus in hypertension, an induced reduction of the normal tonus is desirable in view of the fact that the vascular system is hypersensitive to normal nervous and chemical stimuli; (5) Elevation of the arterial pressure produces wear and tear on the arterial and arteriolar systems, hence reduction of the arterial pressure *per se* is a beneficial procedure.

The following points bearing on these proposals must, however, be considered: (1) as far as cases of essential and of nephritic hypertension are concerned, there is no evidence that increased secretion of adrenalin is present; (2) Similarly, there is no evidence that essential hypertension is of renal origin, and surgical denervation actually fails to influence the state of essential hypertension; (3) There is inadequate evidence up to the present time to suggest that the efferent vasomotor impulses exert a greater constrictor effect in hypertensive than in normal subjects. Recent experimental evidence indicates that the vasomotor tone is not increased above normal in hypertension.<sup>7</sup> (4) If the normal vasomotor tonus could be diminished diffusely in all organs without influencing deleteriously the essential physiologic responses, this would be beneficial. Thus far, however, this has not been accomplished. The decrease of vasomotor impulses within one region of the body, on the other hand, may well have a deleterious effect on the function of other organs in which the constricted state

of the arterioles persists, and in which now, as a result of the decreased blood pressure, a *suboptimal* blood flow will exist (5) The studies of Cannon and his associates<sup>44 45 46</sup> have demonstrated that the blood pressure responses of animals following various types of sections of the spinal sympathetic and splanchnic nerves are not uniform, and that they vary in different species of animals Even after complete exclusion of sympathetic control of the blood vessels the blood pressure, after a postoperative drop, returns to approximately normal level (6) While it is true that elevated arterial pressure represents wear and tear, it is equally true that persistent elevation of the capillary pressure may represent even greater wear and tear on these delicate vessels It should therefore be appreciated that if one induces splanchnic arteriolar dilatation through nerve section, marked capillary hypertension will be precipitated Thus we have shown that the local dilatation of an arteriole with histamine will elevate the normal capillary pressure in hypertension of 12 to 108 mm Hg<sup>9</sup> It is questionable whether the benefit of the moderate drop in the systemic arterial pressure, claimed to result from the denervation, can outweigh the possible damage to the visceral organs, which will have to function under active hyperemia and under increased capillary pressure

Granted that all the foregoing objections, based on experimental and clinical studies, can be obviated, there still remain the following fundamental facts enumerated earlier in this discussion, namely (1) *arterial hypertension is primarily a progressive obstructive disease of the arteriolar system over the entire body*, (2) *the blood flow in the tissues in hypertension is practically always optimal or already suboptimal*, (3) *the elevation of the arterial pressure is a homeostatic adaptation on the part of the body for the purpose of maintaining optimal blood flow to the tissues at rest and under physiologic stress* Suppose one effectively lowers the arterial pressure through splanchnic vasodilatation, one certainly cannot claim to influence the progress of the arteriolar constriction in the brain, heart, muscles and other organs May not these patients ultimately predispose to cerebral and coronary thrombosis? From what we know regarding the compensatory capacity of the peripheral circulation in heart disease,<sup>47</sup> there

may be increased utilization of oxygen for a while and the symptoms may be masked, but the limit of peripheral circulatory adaptation will be reached. Thus, complications, which may be expected, will not become evident within from six to twelve months, the average period of observation in the majority of papers published.

The alleged symptomatic improvement of some patients does not necessarily justify such severe and far-reaching surgical interference as is advocated by many. One may lower the blood pressure and may abolish symptoms, but at the same time may also shorten the life of the patient, who otherwise might have lived for years in fair health. I do not wish to imply that it can be stated definitely that the surgical procedures advocated in recent years are dangerous or indifferent in their results. The conclusion seems justified, however, that adequate evidence as to whether the benefit of surgical measures outweighs their possible harmful effect has not been presented as yet. It is also obvious that some of these measures have been proposed either on false or on unproved premises or without proper appreciation of the clinical nature of hypertension, a condition which shows marked and irregular fluctuations in its course, and in which spontaneous and even permanent lowering of the arterial pressure is not a rare occurrence.

Surgery of the sympathetic nervous system has introduced some significant therapeutic measures, but it has also demonstrated numerous failures, so far as practical measures are concerned. For the practitioner, who primarily cares for the patient, this is important to appreciate. Investigation has to progress through intelligent and justified trial and error. It is wise, however, that physicians should accept therapeutic claims and particularly new surgical procedures only after proper evaluation of the problem and when there is strong supporting evidence. In case of arterial hypertension the presentation of such therapeutic proof is at best difficult. For the present, therefore, it seems advisable to leave the surgical treatment of arterial hypertension in the hands of those surgeons who believe that they can answer the problems raised in this discussion and who can eventually present adequate proof that there is lasting benefit to their patients.

## V CONCLUSIONS

Whereas some of the drugs described are effective in the relief of symptoms in hypertension and of vascular crises or other vasospastic states, an analysis of the evidence presented justifies the conclusion that the majority of them do not fulfill the therapeutic requisites outlined, and that their routine use in hypertension is therefore not advisable.

The value of the surgical procedures practiced recently for the relief of hypertension cannot be considered as established. Several important aspects of this problem have yet to be clarified.

Hence the rational management of hypertension consists in intelligent environmental management of the patient by means of rest periods, diet, psychotherapeutic guidance and sedation. The numerous complications of hypertension should receive specific consideration.

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### THE TREATMENT OF GONOCOCCAL ARTHRITIS, RHEUMATOID ARTHRITIS, AND GOUT

THE current medical literature contains numerous papers concerning the treatment of arthritis. Indeed, it is often difficult to evaluate many of the remedies suggested, since the type of joint disorder is not defined and the natural history of the disease is not taken into account when summarizing the results. It is no exaggeration to say that the adequate treatment of any disease can be carried out only if its cause is known. In many cases of chronic arthritis, and especially the rheumatoid type, the cause remains in doubt so that it becomes necessary to manage the patient in the most practical way. The treatment of any chronic illness is of necessity schematic in type and it must be based upon a rational and conventional diagnosis. In dealing with chronic arthritis, the treatment has the following objectives: (1) the relief of discomforts, (2) safeguarding the patient from deformities and increasing the function of the injured joints, (3) prevention, if possible, of the progress of the disease.

At the outset, it should be remembered that many of the procedures advised by the physician will require readjustment of the individual to the limitation of his or her activity which they must be taught to recognize. This requires considerable thought, tact and sympathy upon the part of the physician, and the best results are frequently obtained by paying meticulous attention to details.

In the evaluation of treatment, one must not forget the natural history of the disease. The question is frequently

asked by physicians—what would be the natural course of events if no particular form of treatment were given? The answer to this question has never been given, since practically all patients with arthritis receive some form of treatment. It is known, however, from the study of large groups of cases, that a certain number of patients, usually around 80 per cent, improve temporarily at least, regardless of the type of therapy employed. In these individuals the disease is relapsing in nature and may continue for years. In others, the disease advances without remissions and in spite of all available treatment. It is well, then, to take these facts into consideration before attaching too much significance to one type of treatment as a method of choice to the exclusion of others.

At this time the treatment of gonococcal and rheumatoid arthritis and gout will be discussed in the light of present-day concepts of these maladies.

### GONOCOCCAL ARTHRITIS

As far as we know, gonococcal arthritis is a true metastatic synovitis, but the tendon sheaths and other tissue of the body may be involved at the same time. The course of the disease, once it is established, may vary tremendously, depending upon the severity of the infection, the joints involved, whether or not reinfection occurs before recovery takes place, and the mode of treatment employed. In any event, the illness may last several months, causing great economic loss and in not a few cases, permanent damage to the joints. In the cases in which permanent damage takes place, there is usually damage to the articular cartilages during the acute phase of the disease, whereas if the disease is confined to the synovia the end-results may be better insofar as function is concerned. The treatment is carried out along the following lines:

- 1 Treatment of the primary focus
- 2 Absolute rest of the joints during the acute phase
- 3 Aspiration or irrigation of joints
- 4 The use of fever therapy
- 5 General upbuilding treatment
- 6 Prevention of deformities

When the knee or other large joints are involved in

gonococcal arthritis, and aspiration of the synovial fluid reveals a leukocyte count above 40,000 per cubic millimeter, and there are micro-organisms present, we usually advise the irrigation of the joint through a small incision in the capsule. It is especially important if the fluid is difficult to aspirate and contains large amounts of fibrin. After the joint has been washed out it is closed tightly, the knee is placed in traction and motion is started as soon as it is possible to do so without pain or discomfort. Our results with this method of treatment have been very satisfactory, with the immediate as well as the ultimate results.

The use of fever therapy either by the injection of typhoid vaccine or other methods has received an enthusiastic reception by many observers. It seems clear from the reported cases<sup>1, 2, 3</sup> that hyperpyrexia seems to be most effective in the treatment of this type of arthritis. Five to seven treatments have been recommended and the temperature is elevated to 106° or 107° F. for five or six hours, every three to five days. The results of various authors have been summarized by Hench, Slocumb and Popp,<sup>1</sup> Schnabel and Fetter.<sup>2</sup> It appears that the best results are obtained in patients with acute gonococcal arthritis of short duration, and less striking results are obtained in the subacute or chronic types of cases. From the reports in the literature it would seem justifiable to use fever therapy in this type of arthritis more often in an attempt to learn more about the ultimate results of the cases treated in this way.

As one observes patients with gonococcal arthritis, it becomes apparent that many of them lose large amounts of weight and develop anemia, the muscles atrophy about the affected joints and the patients present the clinical picture which is so common in chronic infections. In our experience, blood transfusions for anemia and a liberal intake of food is highly desirable in such cases. The general upbuilding treatment is often of the highest importance.

When the above measures are followed, the results of treatment of gonococcal arthritis are usually satisfactory as far as the end results are concerned. The course of the illness is often slow and even with the best of care, poor results are occasionally seen.

The convalescence is often difficult to manage and prolonged, efforts should be directed along the following lines

- 1 Rebuilding muscle tone and strength about the affected joints

- 2 The support of the arches of the feet, especially if the knees have been involved and the patient has been confined to bed for a long period of time

- 3 Instructions regarding venereal disease prophylaxis

### RHEUMATOID ARTHRITIS

The cause of this type of arthritis is unknown. For this reason there is no adequate form of treatment for the condition. It is a malady characterized by remissions and relapses and there is no satisfactory evidence that any of the many remedies suggested are in themselves responsible for altering the course of the process. To be sure, many types of treatment are recommended, so that scarcely a year passes without the introduction of several new remedies. In the present state of our knowledge all one can hope to accomplish is to relieve the patient of as much discomfort as possible, to prevent the development of deformities when possible, and to give the patient the best possible opportunity of recovering from his disease through general upbuilding treatment and the correction of any abnormal functional disorders that may be present. It is highly important to discover, when possible, any factor that makes the patient worse. This can be done by questioning the patient and observing the course carefully. When these factors are discovered they should be eliminated.

**Symptomatic Treatment**—The best form of symptomatic treatment is rest, especially rest in bed or absolute rest of the affected joints. Many patients maintain that the one thing that makes them worse is fatigue. The relief of pain can be accomplished by the use of drugs, the proper application of splints and supports to relieve muscle spasm, and the judicious use of local heat to the affected joints. Of the drugs which give most relief, the various salicylate compounds, and the atophan group are most effective. The latter group of drugs should be used with caution, since one occasionally encounters sensitivity to them.

Splints and support of affected joints should be applied early in order to relieve muscle spasm and prevent deformity. If deformity is inevitable, then the joint should be fixed in the most desirable position. These are problems that must be worked out in cooperation with the orthopedic surgeon.

**General Upbuilding Treatment—*Regulation of Activity***—It is a good plan to keep the patient's joints at rest as long as there are any signs of inflammation present in the synovial membrane. The constant use of a joint which is the site of an inflammatory process only tends to increase the irritation and propagate the process. When the acute process subsides, exercise may be allowed within the limitations of the individual's ability to do work without fatigue or pain.

**Diet**—One of the commonest questions that patients who have arthritis ask the physician is—what can I eat? Some physicians are of the opinion that altering the diet in various ways is of the highest importance in bringing about improvement, but aside from the cases in which there is a definite idiosyncrasy to certain foods there is little convincing evidence that high carbohydrate or other types of diet are responsible for the patient's symptoms. This question has been discussed at some length and in a critical fashion by Bauer, who concludes that "patients with rheumatoid arthritis should take a diet high in calories (unless they are overweight), high in vitamins and adequate in respect to calcium, phosphorus and iron." He points out that there is no convincing evidence that proves that a low carbohydrate diet is indicated in this disease, and that there is no proof that it is efficacious in curing the disease. With these conclusions I am in complete accord.

**Removal of Foci of Infection**—The safest rule to follow in regard to foci of infection is to have them removed for their own sake rather than for the arthritis. By doing this, the patient is sometimes assisted in making a more rapid recovery. Before advising such procedures, definite evidence for the existence of infection should be present and the patient should be informed that such operations may be helpful but they may not necessarily be followed by improvement of the arthritis.



**Miscellaneous Treatment—*Anemia***—When anemia of the hypochromic type is present it should be treated with iron, and in the cases in which it seems desirable to increase the hemoglobin or red blood cells more rapidly, whole blood transfusions may be given. The latter method has been used especially by Dawson and Boots.

***Fever Therapy***—From time to time, various forms of fever therapy are used in the treatment of arthritis, including the artificial induction of fever with malaria, typhoid vaccine, diathermy, hot boxes, air-conditioned cabinets and so forth. Within the past year several excellent reviews of this subject have been presented by Hench, Slocumb and Popp, and Short and Bauer. As far as rheumatoid arthritis is concerned, there seems to be general agreement that the results obtained are of a temporary nature. Short and Bauer report that 80 per cent of their patients showed temporary improvement, but that this was maintained in only 20 per cent of individuals at the end of a two-year period or longer. The patients who seemed to respond most favorably were young individuals with arthritis of short duration, with little or no cartilage destruction, and with marked vasomotor changes who showed an increase in pulse pressure during treatment. They were of the opinion that the improvement in these patients was due to increasing the blood supply to the affected tissues. They concluded that this method of treatment was only occasionally justified and should not be used to the exclusion of general treatment.

From a review of the literature on the subject of fever therapy in rheumatoid arthritis, together with the results of personal observations, Hench, Slocumb and Popp came to the conclusion that the value of fever therapy could not be fully appraised at the present time. They expressed the opinion that a trial of fever therapy is justified in "selected" cases. Of 60 patients treated in this way, 70 per cent got little or no relief and the remaining 30 per cent received significant benefit.

A recent paper by Cecil, Freiss, Nicholls and Thomas<sup>4</sup> relates their experience with malarial treatment of 13 cases of rheumatoid arthritis. All of their patients received temporary symptomatic improvement with disappearance of pain.

and swelling after three or four malarial paroxysms. Within a period of six months after the termination of this treatment, 12 of the 13 patients had a return of their symptoms, but in four of these the general condition was thought to be better than before the treatment. The only patient who had not relapsed during the period of observation had had arthritis only four months before the treatment.

In brief, then, it appears that a small number of patients with rheumatoid arthritis are temporarily relieved following fever therapy. The experience so far would indicate that the improvement is lasting in only a few and that it is most striking in young individuals with arthritis of short duration, with marked vasomotor disturbances, but without cartilage destruction. It should be added that it is a procedure that must be carried out by a physician and a skilled nurse, since it is not an altogether harmless procedure. Hyperpyrexia and death have been reported.<sup>2</sup>

*Vaccine Treatment*—This method of treating rheumatoid arthritis has been used widely for a number of years. In some instances vaccines have been employed to increase body temperature, in other cases, they have been injected in an attempt to increase the patient's immunity to certain strains of streptococci or to decrease his sensitivity to the products of these organisms. The strains of organisms used have been derived from the patient and attempts have been made to select the various strains on a basis of the patient's reaction to skin tests made with these organisms or by determining the presence of complement fixation bodies in the circulating blood. All of these procedures are based upon the assumption that rheumatoid arthritis is due to a streptococcal infection, and while there is some evidence to support such a conclusion, it is far from being settled. This question has been discussed in detail elsewhere and need not be repeated here.

The results of vaccine therapy are controversial. The recent observations of Wainwright<sup>5</sup> indicate that 21 of 28 cases of rheumatoid arthritis showed improvement following intravenous injections of streptococcus vaccine prepared from the strain to which the patient was most sensitive. As objective evidence for the improvement, there was a relief of

pain, a reduction of soft tissue swelling and increased mobility of the joints, together with a uniform decrease in the skin sensitivity and an increase in the agglutinins in the blood of some patients

Boots<sup>6</sup> has recorded the results of his experience by saying that the value of vaccine therapy remains unproved. They have not been able to influence favorably the sedimentation rate of the erythrocytes, and other forms of treatment are followed by as great a clinical improvement as those on vaccine therapy. He expressed the opinion, however, that one can do no harm in trying it.

From the reports of vaccine therapy and from personal experience, it would seem that vaccine treatment should be tried in individuals in whom the arthritis has been preceded by an infection, and in whom one is able to demonstrate agglutinins and skin reactions to hemolytic streptococci. It will be generally admitted that it should not be used to the exclusion of general upbuilding treatment.

*Sulphur Treatment*—Within recent years colloidal sulphur has been used extensively in the treatment of arthritis. A recent paper by Rawls, Gruskin and Ressa<sup>7</sup> records their results with this drug in a miscellaneous group of patients with arthritis, and summarizes the studies of others. They concluded that sulphur was a valuable agent in the treatment of arthritis, in spite of the fact that they did not feel that it was of much benefit in young people with rheumatoid arthritis. When improvement was noted, it occurred in older individuals with rheumatoid arthritis and in patients with "mixed arthritis and osteoarthritis." In these patients the cystine content of the fingernails was said to be low and "sulphur treatment is often beneficial."

One gains the impression from this paper as well as from others that the use of sulphur in the treatment of arthritis is purely empirical and that the evidence brought forth to support its use as a valuable agent in the treatment of arthritis is not very convincing, as far as the ultimate results are concerned.

**Management of Convalescence from Acute Arthritis**  
—This phase of the treatment of arthritis demands great attention since the individual's progress can be accelerated by

intelligent management. Fundamentally it consists in building up muscle tone and the structures supporting the affected joints by exercises and physiotherapeutic measures, and the use of various types of apparatus that may aid in the support of joints. The principles and methods that are used for the different joints have been outlined by Ober,<sup>8</sup> and since the importance of these procedures are in following certain details, his paper should be consulted.

### GOUT

The treatment of gout can be divided into three groups (1) the acute attack, (2) the interval treatment, (3) chronic gout.

By general consent, it is agreed that the pain of acute gout is most severe, and may require large doses of such sedatives as opium to control it. The following procedures should be carried out: (1) Rest in bed. (2) Protection of the affected joints. (3) Forcing fluids to 3000 cc. a day. (4) Administration of purges in the form of wine of colchicum and tincture of rhubarb until a free diarrhea is obtained. (5) The use of atophan, alkalies and salicylates. (6) A diet that is high in protein and carbohydrate but low in fat and purine.<sup>9</sup>

Once the acute attack has subsided, it is well to advise the patient regarding factors that aid in preventing attacks. In many cases, the patients with gout know only too well what brings on their attacks, in others, they, as well as the physician, are unaware of the cause of an acute attack. Such conditions as dietary indiscretion, excessive fatigue or trauma to the various joints should be avoided. In addition, adequate care should be taken to see that these patients remain on a low purine, low fat diet with liberal amounts of protein in the form of milk, eggs, cheese, and an adequate amount of carbohydrate. Alkalies, salicylates and cincofen are also recommended in small doses and the fluid intake should be such as to give a dilute urine. Since these patients often have attacks following surgical operations, they should be prepared before operation by the treatment outlined above and by a low purine diet.

**Chronic Gout**—The measures outlined above are used in the treatment of chronic gout, but in some cases in which

there are large deposits of urates in and about the joints, the treatment is unsatisfactory. I have recently observed a patient who has had attacks of gout for forty-six years, and at present he is completely incapacitated on account of the great deformity of his hands due to the deposits of urates, the destruction and ankylosis of some of the terminal phalanges. He informs me that only two things give him relief, one is colchicum and the other is the relief of tension in the affected joint that follows a puncture wound and the expression of urates. In these cases, treatment continues to be unsatisfactory and the nature of the disease needs further investigation.

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### TREATMENT OF DISEASES OF THE THYROID

I HAVE been asked to give a clinic illustrating by means of cases some of the problems involved in the treatment of diseases of the thyroid—recent advances in the treatment of these diseases, in fact I am not aware of any very recent advances in this field, at least, none that have got beyond what might be called an experimental stage. It is greatly to be hoped that we soon shall have a nonsurgical method of curing thyrotoxicosis and from the interrelationships of pituitary thyrotropic hormone and antihormones, in the sense of Collip, should the existence of these finally become well established, we have reason to hope that a nonsurgical treatment will presently emerge. Reports of remedies of this kind are to be found in the German literature, but their value has certainly not yet been established beyond all question. From a practical point of view we still find ourselves in the situation we have been in for some years, which is that subtotal thyroidectomy, during a period of full iodization is the best therapy we can advise for our patients suffering from toxic goiter.

Nor has anything very new recently emerged in the treatment of myxedema. In dried thyroid gland we have for years possessed an ideal treatment for the hypothyroid states and experience over a number of years has indicated to us that the wisest policy to follow is that of placing the patient on the minimum ration of dried thyroid, by mouth, which will rid him completely of all symptoms and signs of myxedema.

In the field of thyroid diseases not accompanied by change

in the function of the gland, which includes simple goiter, nontoxic nodular goiter, malignant goiter and inflammatory goiter, the principles of treatment consist in surgical removal when any of the following indications are present (1) pressure, (2) suspicion of malignancy, or (3) unsightliness which troubles the patient, and occasionally irradiation in some form or other, either alone or in conjunction with surgery, in certain of the malignant cases

It obviously is impossible, in the space allowed, to illustrate by cases all these different problems. Because the routine care of the various types of thyroid disease has been thoroughly discussed in previous clinics in this series as well as elsewhere,<sup>1 2, 3 4, 5, 6</sup> I have decided that the best use to which to put the present clinic is that of illustrating how one works out the indications for treatment in some of the puzzling, complicated or atypical cases

Let us begin with the case of Miss B. This patient, a lady of forty-three, consulted me first on March 25, 1935. She had had a subtotal thyroidectomy for exophthalmic goiter in a Middle Western city in February of 1933. In the autumn of 1931 she had had grippe and following this was in a rundown condition. Metabolic tests had been made showing a result of  $-7$  and thyroid had been ordered. She had taken this for six weeks. According to her story it had had no noteworthy effect. In the summer of 1932 she had taken a trip abroad and had become very fatigued as a result. For this she again took thyroid intermittently. In the autumn of 1932 it was found that she was losing weight rapidly and having rapid heart action. She was seen in a private clinic in Boston and states that she was there told that she had no thyroid trouble. She continued to feel badly, however, and while visiting in the Middle Western city the diagnosis of exophthalmic goiter was made and operation performed as I have already stated.

Following her operation she was better in general but it took a very long time for her to get her strength back. She had been placed on Lugol's solution prior to the operation and had continued to take it ever since. During the year before I saw her, her eyes had become increasingly prominent. Her major symptom was fatigue. During the autumn of 1934 she had been so exhausted that she was almost bedridden for three months. She not infrequently had palpitation, but didn't sweat much. She had lost 3 or 4 pounds since the previous Christmas. Two weeks before she came to me she had a bout of diarrhea. She had had such bouts before operation but none since. Her catamenia were regular but scanty and brief. There was nothing in her past or family history that seemed to be significant.

My physical examination on March 25, 1935 showed a startled looking, middle-aged, thin woman who did not act in the slightest degree as though she had thyrotoxicosis. She had bilateral exophthalmos, more on the left than on the right, of moderate degree, bilateral lid lag, but no irritation of her corneae. She had no tremor and her hands were cold and dry. No thyroid

tissue could be palpated no bruit could be heard in the neck but a thrill could be felt in the region of the right lower pole of the thyroid. Her heart was rapid—rate 100 but not enlarged rhythm was normal and there were no murmurs. Her blood pressure was 110/90. The remainder of the physical examination showed nothing of significance. She gave the impression of being a very lackadaisical languid person. I may add that she was a lady of means and leisure, apparently without responsibility whose chief interests in life were gardening music and church work.

It was my very definite impression when I first saw her that she was not thyrotoxic, that she had no return of her Graves disease and that her symptoms were upon a psychoneurotic basis—something which might be called perhaps for want of a better name effort syndrome. I was convinced that she had had exophthalmic goiter in the past because of the presence of the definite eye signs.

I obtained a metabolic rate determination which on April 2 1935, showed levels of  $-5$  and  $-10$  for two consecutive periods. This seemed to square with the impression that she was not thyrotoxic. I ordered her to stop her iodine and then sat tight to see what would happen. What did happen was of great interest. On April 12 her metabolic rate had risen to  $+17$  and on April 13 it was  $+25$ . Coincidentally with this her symptoms became greatly intensified. She became weak to the point of exhaustion and her pulse rose to a level of about 115 her skin became warm and sweaty. At this time a small amount of thyroid tissue was felt in the region of the isthmus.

The picture therefore had undergone an important change since the omission of iodine. There seemed little doubt at this time that she was thyrotoxic and that this thyrotoxicosis had supervened upon the omission of iodine. The natural further deduction was that she had been potentially thyrotoxic all along probably ever since her operation but that this thyrotoxicosis was a residual of rather small proportion which the ration of iodine was able to hold partially in abeyance. Dr Arthur W Allen was called in consultation and he agreed that the case was probably one of persistent and recurrent thyrotoxicosis and that further resection of thyroid tissue was indicated. A second operation was done on April 23 1935. This operation was subtotal thyroidectomy upon the remaining tissue. A piece of thyroid about 5 cm long 2 cm wide and  $1\frac{1}{2}$  cm thick was dissected out from the neighborhood of the right side of the trachea and the region of the isthmus.

The histologic picture of this removed tissue was that of definite parenchymatous hyperplasia with considerable colloid storage in places. This anatomic finding therefore confirmed the clinical impression of recurrent exophthalmic goiter.

The patient went through the operation very smoothly and on May 1 1935 the metabolic rate was  $-11$  on May 6 it was  $-20$ . At this time the patient was still taking iodine—Lugol's solution, 5 minims once daily. On that day she was discharged from the hospital and iodine was omitted.

I have seen her from time to time since and on the whole she has been considerably improved although there are periods when her old feeling of weakness seems to return. On September 24 1935 metabolic rate was  $-15$ . I saw her on that date and my impression was that she was essentially well.

This case impresses me as being distinctly instructive. In the first place it was proved that persistent or recurrent thyrotoxicosis was present in spite of the fact that the patient



was running a metabolic rate below standard and presented symptoms which were by no means characteristic of thyrotoxicosis. Treatment necessarily hangs upon diagnosis. In this case the diagnosis was established by means of an iodine test carried out in a manner the reverse of that usually practiced, instead of noting the result of giving iodine, in this case, we noted the effect of omitting it. As soon as it was omitted the low grade thyrotoxicosis which the iodine had masked, manifested itself quite clearly.

On the first consideration of the case it would have seemed ridiculous to propose a second thyroidectomy for toxic goiter when there were no thoroughly characteristic symptoms, a slightly minus metabolic rate and very little thyroid tissue to be felt. None-the-less, it turned out that that was the correct treatment and the final result has proved this.

One may draw the general conclusion that before planning treatment in any thyroid case, the true level of functional activity must be determined and oftentimes this can only be done by giving or omitting iodine, or indeed doing first one and then the other.

Let us next consider the case of Mrs B, a woman sixty-nine years old, who entered the hospital under my care on June 15, 1934, referred by Dr Paul D White. Dr White had had this patient under observation since October, 1927, at which time he had made a diagnosis of irritable, slightly hypertensive heart with many ventricular premature beats. He had also observed at that time a slight enlargement of the thyroid with slight bruit. He had seen her at intervals since and she had always shown ventricular premature beats and some nervous symptoms. Nothing had happened, however, until a few weeks before entry when seeing her at her home Dr White found she was losing weight rapidly and having tachycardia with many premature beats and a very full pulse pressure. He considered that thyrotoxicosis was very likely present.

Upon Mrs B's entry to the hospital I did my best to decide at Dr White's request (1) whether she was thyrotoxic, and (2) whether, if she were thyrotoxic, she was fit for operation. My physical examination at the time of entry disclosed a woman, not obviously hyperactive with none of the eye signs of exophthalmic goiter, with very slight tremor and with a thyroid isthmus and lateral lobes just barely palpable. Her heart was enlarged and fibrillating. No gross edema could be found anywhere. She was not orthopneic. The remainder of the physical examination was not highly informative.

She was put to bed and observed. The following metabolic rates were obtained: June 16, 1934, +33, June 19, +39, June 21, +35, June 23, +38, and June 26, +34. The maintenance of this elevated level in the absence of gross congestive heart failure was strong presumptive evidence of thyrotoxicosis. It was determined to observe the effect of giving iodine. After five days of

iodine, no fall whatever was noted in the metabolic rate level. The iodine was begun on June 22. Digitalis had been begun the day before. Under the influence of these two drugs the pulse rate slowly fell from a rate of about 120 to one under 100. There was no means of determining which drug was chiefly responsible.

I had been very dubious of the evidence of thyrotoxicosis at entry and recorded that opinion in the hospital record; however, after observing the level of metabolic rate I began to question the accuracy of this conclusion. The failure of her metabolism to drop in five days on iodine was inconclusive one way or the other. Further metabolic rate determinations should have been made but since the tests distressed the patient considerably they were omitted.

Because of Dr. White's feeling that the heart condition was best explained by thyrotoxicosis, and because the surgeon who saw the patient in consultation believed that he could do a thyroidectomy successfully (he stated the risk was about five times the normal however), and because the family were eager to leave no means of treatment unused that offered any hope of relief, I finally consented to operation on her thyroid. This was done on July 2, 1935. The operation itself went extremely smoothly. The patient returned to her room in excellent condition. The operation actually was a subtotal thyroidectomy. There was found at operation a very small right lobe also an enlarged isthmus, a moderately sized pyramidal lobe on the left and a large left lobe. The patient did not long continue to do well after operation. She became gradually weaker, her pulse and temperature steadily climbed and she died the third day after operation. Unfortunately no autopsy could be obtained.

Finally a very important finding was that the pathologic examination of the thyroid showed no evidence of hyperplasia, merely the picture of colloid goiter or so-called involution. As we look back over this case we can not escape the feeling that the operation was very likely not indicated. We learn by our errors. One error here was certainly in terminating the period of observation before the response to iodine or lack thereof had been definitely established. But even had this been done we might still have found ourselves in difficulties. How would we have interpreted a persistently high metabolic rate in spite of full iodination? One interpretation would have been that thyrotoxicosis was not present. One cannot however, say categorically that failure to respond to iodine absolutely excludes overactivity of the thyroid. There are cases undoubtedly thyrotoxic, who fail to show an iodine response perhaps because the iodine is given at a time when their thyrotoxicosis is undergoing natural intensification. Mrs. B's story would have been consistent with such an interpretation. Had a good response to iodine been obtained, we should have felt that the indication for operation was much clearer. It is a pity that we didn't carry on long enough to give an opportunity for an unequivocal answer to our test. It is doubtful whether had we left her unoperated she would have lived very much longer. The cardiologists' opinion was that her outlook without operation was distinctly poor. That was one reason why it seemed rational to take a fairly desperate chance. In retrospect I regret that an operation was undertaken. I should rather have had her die unoperated than apparently as a result of surgery. The question also comes up as to whether multiple operation might have been better for her. I think this is possible but not likely. It is my belief that the same outcome would have obtained had only a small portion of the goiter been removed as a preliminary procedure. This however is a point which cannot be settled.

Let us pass now to the case of Mrs M, which I should like to contrast particularly with the case of Mrs B. Mrs M, a widow of fifty-nine, entered the hospital on November 29, 1934. She came in complaining of nervousness and fatigue for several months, emotional instability and recent weight loss. On physical examination she showed a warm, moist skin, definite tremor of her fingers, an enlargement of the isthmus and left lobe of the thyroid, but no eye signs characteristic of exophthalmic goiter. It was not possible to say, on the evidence which she presented, that thyrotoxicosis was present but there was a very definite suspicion of it. On November 30 her basal metabolic rate was found to be +49 and it was determined to conduct a diagnostic test with iodine. After iodine had been started the following metabolic rates were obtained: December 1, +47, December 3, +37, December 4, +42, and December 5, +40. On the latter day iodine was omitted. On December 10 the metabolic rate was +28, on December 12, +48, on December 13, +34, on December 14, +39, on December 15, +38, on December 17, +32 and on December 18, +32. On December 21 iodine was started again—potassium iodide, 10 minims once a day. On December 22 the metabolic rate was +46, on the 26th it was +40, on the 29th it was +43, on the 31st it was +31, on January 2, 1935, it was +30 and on January 4 it was +31. In other words, there was absolutely no indication that her condition was better while taking iodine than while not taking it. The iodine test was frankly negative. Nevertheless, it was felt that the clinical picture better fitted thyrotoxicosis than anything else and as the patient was not improving it was finally decided to resort to surgery. On January 5, 1935 a subtotal thyroidectomy was performed, which the patient stood very well. A considerable portion of both lateral lobes and isthmus was removed. The histologic examination of the tissue removed showed the type of hyperplasia characteristic of exophthalmic goiter with considerable colloid storage, that is to say involution. The patient made an uneventful recovery and on the 16th of January her metabolic rate was +2.

Mrs B's case and Mrs M's case furnish some interesting similarities and contrasts. The metabolic rates of the two were running at about the same level and in neither case did we establish any improvement as a result of giving iodine. We held off on Mrs M's operation for a considerable period of time, largely because of the experience with Mrs B. I felt that the failure to respond to iodine might, on the one hand, indicate that she wasn't thyrotoxic or, on the other, that if thyrotoxic she would be a poor operative risk. Both of these interpretations were incorrect. It turned out that she was definitely thyrotoxic and she did go through operation very smoothly. The presence of the serious heart disease in Mrs B, of course, made the problem a much more difficult one than in Mrs M, whose heart was apparently normal. Taken together, the cases may be said to teach us that while the iodine test is very helpful, it is not to be looked

upon as finally giving the absolute indication to treatment in all cases. In this respect it is not different from any other diagnostic test which we employ for a similar purpose.

We may now pass to another case, this one of proven thyrotoxicosis which presented some interesting difficulties. Mr S., a widower of forty six entered the Massachusetts General Hospital first on November 26 1934 transferred from the Boston Psychopathic Hospital to which institution he had been sent two months previous for some definitely psychopathic manifestations. In addition to these however he had an array of signs and symptoms classic of exophthalmic goiter and it was for that reason that he was sent to us. Examination and history further disclosed that he was suffering from rheumatic heart disease with involvement of both mitral and aortic valves, congestive heart failure and auricular fibrillation. He had moderate exophthalmos and lid lag a very wild expression a small firm goiter with very loud bruit, warm skin which was moist except in the palms which were dry, and slight edema of the ankles. The diagnosis of exophthalmic goiter was evident and also the complication of rheumatic heart disease with decompensation, and apparent psychotic manifestations.

When I first saw him I felt he should be iodinated at once and operated as soon as he was ready. I felt that to rid him of his thyrotoxicosis might rid him of all his troubles—thyroid, cerebral and cardiologic. His metabolic rate on November 27 was  $+43$  and on November 30  $+53$ . He made a good response to iodine his metabolic rate dropping to about  $+30$  and his symptoms showing marked improvement. He had a good diuresis, losing 10 pounds of weight, which was presumably water and showed an amazing improvement in mental state. We felt that he was ready for operation when he developed a throat infection which necessitated its postponement. To make a long story short, this dragged on and on and to it was added a certain amount of bronchial infection which caused him to run a temperature of low grade for many weeks. During all this period iodination and digitalization were maintained. Also during all this period his mental state seemed to be quite normal. It was our belief that his psychosis was purely a manifestation of thyrotoxicosis. Finally on the 18th of March 1935 his infection having subsided considerably an operation was performed. Because the surgeon was worried about his condition on the operating table, the removal was confined to the right lobe and isthmus in other words, hemithyroidectomy. Histologically this tissue showed slight hyperplasia and marked involution. This doubtless was due to the prolonged iodination. He was discharged from the hospital on March 26 afebrile and in pretty good clinical shape but with a metabolic rate still running at a high level—in fact, higher than before his hemithyroidectomy. Metabolic determinations had not been made for some time prior to the operation because of the presence of infection. After the operation they were running in the neighborhood of  $+60$ . The circumstances of his admission required that he be returned to the Boston Psychopathic Hospital for further observation although during his long stay in the Massachusetts General Hospital he had shown no symptoms which impressed us as indicating any mental abnormality except those described just after admission.

On July 19 he was readmitted to the Massachusetts General Hospital to have a second operation upon his thyroid. At that time he seemed to be in very good condition had gained 28 pounds and was showing no evidence of psychosis, but still had a metabolic rate in the  $+60$ s. On reiodination this

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dropped to a level of  $+20$  and on August 6 his second hemithyroidectomy was performed. This he survived very well and on August 20 his metabolic rate was  $-2$ . On August 22 it was  $-13$ . Since then it has varied somewhat, often being within normal limits, but occasionally being up as high as  $+28$ . Following this second operation the patient became very much depressed and although this slowly improved, on October 18 he suddenly became violent and was discharged once more to the Boston Psychopathic Hospital.

This case brings up three factors which complicate the treatment of thyrotoxicosis: cardiac decompensation, mental decompensation, and respiratory infection. Indeed, we might add a fourth, namely, condition of the patient on the operating table which makes the surgeon unwilling to do more than a hemithyroidectomy.

I use the term "mental decompensation" advisedly. Just as the thyrotoxicosis adds a burden upon an already overloaded heart (overloaded by independent heart disease), so too may it add a burden to a brain potentially the seat of a psychosis and precipitate the same. As it has turned out this man seems to have a true chronic psychosis. Nevertheless, there is little doubt that the thyroid intoxication, working on such soil, created unusual havoc. Either the cardiac or mental complications in this case should be looked upon as indication for hastening operation to rid him of the extra burden which we have a way of removing.

The respiratory infection, upper and lower, which dragged on all winter, on the other hand, necessitated postponement of operation. However, by patiently waiting and maintaining iodination even this obstacle finally was overcome.

Finally, hemithyroidectomy is an unsatisfactory operation, because often it is necessary, as here, to follow it with a second resection. It is unpleasant, to say the least, for a patient to have his goiter out piecemeal.

This illustrates some of the vicissitudes of treatment. In spite of the several complications the outcome was good in all respects, except that there remained a residual psychosis, to which the psychiatrist gave the name of manic depressive.

The last case which I shall discuss presents a problem of quite a different nature. Mrs. S., a widow of sixty-six, entered the Massachusetts General Hospital first on June 22, 1922. Her story at that time was that for eight months she had gradually been losing strength and ambition and that occasionally she

had had attacks of dizziness. Furthermore she had noted some swelling and puffiness in her face and her vision had appeared to her to be less acute. She had had increasing constipation and her skin had been getting dry and yellowish. These seemed to be the essential points in the history. Physical examination showed her to be obese and her face to present a strong suggestion of myxedema. The basal metabolic rate was determined on two occasions showing results of  $-34$  and  $-35$ . Her urinary and blood pictures were both within the range of normal. I was asked to see her in consultation the particular question being did I think she was suffering from hypothyroidism and if so what therapy should she be given. My reply as it stands in the hospital record dated June 28 1922, is as follows: "Yes, in spite of certain atypical features, I think myxedema is very probably the trouble. I should get another metabolism test and then start her on  $7\frac{1}{2}$  grains of Burroughs Wellcome thyroid and in a week have another metabolism test. After that regulate dose in accordance with clinical picture and metabolism level."

It may be worth while to comment on the dose of thyroid which I then advised. Seven and a half grains is a perfectly proper dose of Burroughs Wellcome thyroid. Since this firm gives its dosage in terms of fresh gland it is different from the dosage which would be used of a brand of thyroid which conforms to the United States Pharmacopoeia. It appears to be the total organic iodine content which determines the physiologic potency of thyroid preparations. Our study of various commercial brands of thyroid indicates that the following are approximately the same both as to iodine content and as to physiologic potency: Burroughs Wellcome 5 grains; any U S P brand such as Armour's, Lederle's, Hynson Westcott and Dunning's or Lilly's, 1½ grains; or Parke Davis 1 grain. Therefore the dose that I advised of Burroughs Wellcome thyroid would be equivalent to a 2½-grain dosage of any U S P preparation.\* This is a little larger ration of thyroid than we advise at the present time. Our present custom is to use about 1 to 1½ grains of U S P thyroid. In 1922 we rather felt that it was desirable to give enough thyroid to raise the metabolism to standard. At present we are content merely to rid the patient of symptoms, which can be done with such doses as I have just mentioned. Under these circumstances the metabolic rate is apt to be in the neighborhood of  $-10$  to  $-15$ .

Mrs. S. was placed on the dose of thyroid which I advised and her myxedematous manifestations cleared up. Thyroid was begun on June 30 1922 and six days later her metabolic rate had reached  $-19$ . She was kept on this dose of thyroid until July 10 when it was raised to 12 grains of Burroughs Wellcome per day. She was discharged from the hospital on July 15 1922 and on July 28 when she came into the clinic her metabolic rate was found to be  $-2$ .

She was seen from time to time in the clinic and remained well thyroid therapy being continued. In February 1923 her metabolic rate was  $-3$  and in April of the same year it was  $-4$ . She then was lost sight of for a period of eleven years until December 2 1934 when she was again admitted to the ward sent in by a private physician. The story at this time was that she had continued taking thyroid somewhat irregularly. One year before this time she had begun to notice swelling of her ankles, which had gradually increased. Seven months before she had become weak in the legs and had massive edema which made it hard for her to get about. At this time she stated her physician told her she had heart and kidney trouble. He put her back on thyroid but she says that it didn't give her much relief. At the same time she was put on digitalis. Two months prior to the last entry she began to have increas-



ing thirst and increasing micturition. Finally her physician told her that she had diabetes and sent her into the hospital.

Physical examination showed her to be very obese, with somewhat dry skin which had a faint yellowish tinge. Her heart was somewhat enlarged with a rough blowing systolic murmur heard loudest at the second right inter-space. The liver edge was felt  $2\frac{1}{2}$  fingerbreadths below the costal margin and there was marked pitting edema of both legs. Her urine showed a moderate amount of sugar and her fasting blood sugar on several occasions was over 200 mg. My note on December 14 was as follows: "She apparently stopped thyroid about two months ago. She probably is coasting downhill metabolically. Now has -25 basal metabolic rate which is a level of slight symptoms. If kept off thyroid, presently she will have symptoms. I should give her no thyroid till symptoms show up and then put her on a very small ration, say  $\frac{1}{2}$  grain (U S P) once daily." I saw her again on January 4, and made the following note: "She still presents no clinical evidence of myxedema although off thyroid. Her diabetes is controllable thus far by diet alone. Her fasting blood sugar level is gradually falling. She may be continued off thyroid until clinical evidence of myxedema turns up." On January 8 Dr. J. H. Townsend, chief of our Diabetic Clinic, saw her and made the following note: "It seems as if she could be managed without insulin when she goes home. She is losing weight gradually on her present diet which should be continued pretty strictly." On January 11 she was discharged with a diagnosis of myxedema and diabetes mellitus. She was discharged with no medication and with a diet of C 82, P 58, F 64. Her metabolic rate at this time was -23. We didn't see her again until August 26, 1935, when she was readmitted to the hospital. She had grown progressively weaker, had increasing constipation, puffiness of her face, dryness and scaliness of her skin, decreased tolerance to cold and diminution in the acuity of hearing. On physical examination she now had, in contrast to the previous entry, the appearance of full-blown myxedema. She was very bloated, with sallow yellowish complexion, round puffy face, coarse hair, sparse eyebrows, slow thick speech and big tongue. Her metabolic rate on August 29 was -30 and on August 30 -34. Her urine, however, showed no sugar and her blood sugar was 100 mg. I saw her on September 4 and made a note as follows: "She is definitely myxedematous now and apparently her diabetes is practically gone. Her heart also is behaving well. I believe the thing to do now is to place her on a small ration of thyroid, 1 grain per day. This will not totally abolish her myxedema, but should relieve it considerably and at the same time not be large enough greatly to aggravate her diabetes or cardiac weakness. I should carry on with thyroid alone in order better to evaluate its effect. Later if digitalis seems indicated it can be added."

These directions were carried out. She was placed on a ration of U S P thyroid, 1 grain per day on September 6, after which basal metabolic rate determinations were as follows: September 12, -34, September 16 -26, September 17, -32, September 21, -23, September 24, -19, and September 29, -23. She brightened very noticeably during this time and the myxedema facies disappeared. The fasting blood sugar had risen to 169 mg on October 4, although no glycosuria had appeared. The development of some mild angina pectoris led to the omission of thyroid on October 2, following which the angina disappeared and the basal metabolic rate dropped back to -29 on October 7.

On October 10 thyroid was resumed in smaller dosage,  $\frac{2}{3}$  grain once daily. She has remained on this dose since and has kept essentially free from the symptoms of myxedema, diabetes or angina.

This case illustrates how two diseases may be inimical one to the other. I do not mean that each aggravates the other but that each has the effect of diminishing the intensity of the other. Thus in this case the more myxedematous the patient became the less was she diabetic and as her myxedema was relieved by thyroid the more did she become diabetic. Also getting too far away from myxedema occasioned attacks of angina.

It will be recalled that Wilder<sup>9</sup> and Blumgart<sup>10</sup> have produced myxedema artificially as a form of treatment for severe diabetes. In our case nature has done something similar, except that the myxedema antedated the diabetes. The therapeutic problem in such a case is an interesting one, namely, so maneuvering as to steer between the Scylla of myxedema and the Charybdis of diabetes. By the use of a smallish dose of thyroid this was accomplished successfully.

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### TREATMENT OF SCARLET FEVER AND DIPHTHERIA\*

#### SCARLET FEVER

THE treatment of scarlet fever resolves itself primarily into a consideration of serum therapy, the theories of its applicability, and the results obtained from its administration in the course of the disease. The surgical complications which arise in its course will be touched upon only insofar as they concern the physician in attendance. A consideration of the origin and nature of the complications is an essential background for treatment, whether medical or surgical. Unfortunately, our knowledge in this respect is far from being satisfactory, consequently, our ideas must always be subject to rearrangement when theories are not substantiated by clinical experience. This statement applies equally to the medical man and to the surgeon who venture to deal with the problems of scarlet fever.

#### SERUM THERAPY

It is necessary to bear in mind that scarlet fever is an expression of a reaction to the invasion of certain strains of hemolytic streptococci. These strains have two very distinct properties. The first is peculiar to these particular strains, namely, the toxin producing property. The second is the

\*The author has purposely avoided detailed accounts of cases of scarlet fever and diphtheria because of the wide variety of manifestations exhibited in these diseases and also because the practitioner who is interested in this subject can easily call to mind from his own experiences cases in which the subject matter of this article applies.



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pyogenic or pus-forming property, which is shared by hemolytic streptococci in general

The toxins of the scarlet fever strains produce the primary inflammation of the fauces, the enanthem on the soft palate, the strawberry tongue, and the rash on the skin. The rash consists of capillary dilation with enlargement of the papillae, and is associated with a tendency to minute hemorrhages according to the grade of toxicity in the individual attacked. These ruptured capillaries are most pronounced in the folds of the axillae and groins. We are justified in the inference that there is coincidental endothelial cell damage along with this process, and that the results of this damage may play a part in the subsequent course of the disease. The symptoms of vomiting and fever accompany the toxemia. In this connection Hektoen<sup>1</sup> has observed that "the toxin of scarlet fever streptococci is something more than erythrogenic" in that in susceptible persons it produces other symptoms than those by which we diagnose the disease. This, in brief, is the picture produced by the toxins of these scarlet fever strains.

It is the isolated toxin, or a combination of these toxins, which serves for the Dick test and immunization purposes, and by which we obtain antitoxin from the horse. While it was hoped that bactericidal and antipyrogenic substances would be obtained in the antisera—especially by means of the Dochez method—clinical experience does not substantiate this to the degree in which our hopes were raised. Consequently the direct effect of antitoxin is confined to neutralization of the toxin. When antitoxin is used early enough, preferably in the first twenty-four hours and not later than forty-eight hours after the onset, the effect is usually dramatic in the relief of the toxic symptoms. On this point almost all experienced authors are agreed. The fever drops, the rash fades, and the throat is improved. In fact, it is a common experience to have these cases so greatly improved the following day that only traces of the disease are apparent. This same thing can be achieved by the administration of convalescent scarlet fever serum or by transfusion from a convalescent scarlet fever donor.

This brings us to an important point in the discussion. During the past fifty years the mortality from scarlet fever has been steadily dropping in America and England. Patients

rarely die from toxemia, but they suffer greatly and die from a wide variety of complications. Therefore, it is to the complications that we must turn our attention. It is in this field that we become aware of our lack of knowledge and the resulting disagreement as to the value of therapeutic measures.

The complications of scarlet fever may be divided into those which are of pyogenic origin such as abscess formation, and those which are not, such as arthritis, glomerulonephritis, and purpura hemorrhagica. Again, they may be divided into those which appear with the eruptive stage and those which take place after the acute symptoms have entirely subsided. Lymphadenitis, otitis media, sinusitis, and purulent rhinitis are common in the eruptive stage, yet they often appear rather suddenly at any time during convalescence. Glomerulonephritis and purpura hemorrhagica, however, are more apt to come on abruptly somewhere around the fourteenth day.

The significance of these two classifications of complications is appreciated by the clinician, although he has no clear explanation in mind as to why otitis media, for instance, can take place at the onset when there is every reason to suppose that it is a direct extension of the throat infection, and why exactly the same type of otitis media can occur in the third week of convalescence when, to all appearances at least, the throat and nose are normal and the patient seems on the high road to recovery. This latent phase in scarlet fever is a most perplexing problem, and has called forth an array of theories, none of which is satisfactory. In fact, I am not at all sure that the origin of the early complications is as simple as we try to make it. I have observed an earache with injection of the drum following each weekly injection of the toxin during immunization. Seiferth<sup>2</sup> goes so far as to say that in every case of scarlet fever, hyperemia of the tympanic cavity takes place in the eruptive stage. However, the possibility which all this implies as to the toxic element in the initial stage of early otitis media does not help us to understand the origin of late otitis media when the toxin, to all appearances, is thoroughly neutralized. Furthermore, otitis media can originate while a patient is experiencing that beneficial effect from the early administration of antitoxin. Thus, while complications can well arise from the direct action of



the toxin alone, they may also arise from the penetrating and pyogenic properties of these streptococci. These latter properties may possibly be indirectly related to endothelial cell damage. The effects of this damage might occur early or late in the disease and would not be influenced by the presence of antitoxin, whether spontaneously or artificially supplied.

The effect of serum therapy on the complications of scarlet fever may be divided into two categories. First, it has no appreciable effect on complications, once these have made an appearance. Second, its early administration is not attended universally with any marked lessening of complications. This statement bears qualification. Antitoxin is not of the same standard potency the world over. In spite of the greatest care in preparation, standardization, and aging, different lots of serum from even the same laboratory vary in their efficacy and in their incidence of serum sickness. Convalescent serum varies greatly in its efficacy, and it is not standardized. If pooled serum is used, the antibodies for the offending strain may be sufficiently diluted by the mixture to be quantitatively ineffective.

While antisera are generally effective in combating toxemia, the divergent results in preventing complications can, at least in part, be attributed to the type of serum used, the dosage, and the method of administration. At the scarlet fever congress in Königsberg in 1928 the great majority expressed the opinion that antisera did not prevent complications.<sup>3</sup> More recently, numerous European and the majority of American and English authors report favorable results in this respect in reasonably large series of cases. Toomey<sup>4</sup> has pointed out that in 4611 serum-treated cases recorded in the literature only 26 per cent were controlled by cases from the same epidemic. Toomey found slightly more complications in his serum-treated cases than in the untreated. Nor is his unfavorable experience unique. Kohn and Josey<sup>5</sup> found intramuscular use of Dochez serum ineffective in preventing complications. Cinca<sup>6</sup> and his coworkers in Roumania, where the disease is still severe, Rolleston<sup>7</sup> in London, and Gabriel<sup>8</sup> in Vienna, where the disease has lost much of its toxicity, give little credit to antitoxin in this respect.

At the Haynes Memorial in an analysis of 10,000 cases of scarlet fever we have compared by two different methods the incidence of complications with and without serum. Using the pre-serum period as a control we found 15 per cent more complications than in the period where serum was given. During the serum period about one third received serum and these showed 5 per cent more complications than those receiving no serum. In the first method we have to discount the fact that the disease has been growing less severe, in the second we have to recognize that all the very mild cases received no serum. These two factors make it difficult to evaluate the effect of serum therapy on the incidence of complications, in spite of the very dramatic improvement in the toxic symptoms shown by so many of these serum treated cases.

On the other hand, Place,<sup>9</sup> Gordon<sup>10</sup> and his coworkers,<sup>11</sup> Stevenson<sup>12</sup> and his coworkers, Craig,<sup>13</sup> Friedemann,<sup>14</sup> Hunt,<sup>15</sup> and Banks<sup>16</sup> have reported decidedly favorable results in preventing complications. Hoyne<sup>17</sup> and Bahov<sup>18</sup> have found convalescent serum definitely effective in preventing complications.

Granting that complications have been materially lessened in the hands of most competent observers, there is still to be considered the disadvantage of serum sickness from antitoxin. Numerous authors have pointed out that the routine use of antitoxin in all cases causes more hours of illness in the mild cases than these would ordinarily suffer if not given serum. Consequently we must weigh the good we expect to accomplish with the possibility of serum sickness. Having had three severe Arthus reactions from scarlet fever antitoxin during the past winter, my enthusiasm has been somewhat dampened. It is difficult to reconcile the remark of Banks<sup>16</sup> that he encountered no serum sensitive patients in his intravenous series with a later remark in the same article that 3 cases suffered from shock after one lot of serum. Place<sup>9</sup> has seen 125 Arthus reactions from antiscarlet and antitetanus serum. The unbridled enthusiasm of some authors<sup>19-20</sup> reminds me of my own first impressions.

In talking with others of hospital experience I find a growing tendency to reserve serum therapy for severe cases and to favor convalescent serum. There are two disadvantages in convalescent serum. First, as has already been mentioned, it is not standardized, and it sometimes does not contain enough antibodies for the offending strain. Second, it is not obtainable by the general practitioner, except where there are serum centers, as in Detroit and Chicago. Elsewhere the

general practitioner is at the mercy of those who control the supply

Lichtenstein<sup>21</sup> reports an interesting analysis of 1000 cases equally divided into antitoxin, convalescent serum, and no serum. He attributes his infrequency of serum sickness to the fact that the Swedish serum is not concentrated. The incidence of complications was only very slightly reduced in both of the sera groups.

It is to be hoped that a marketable product will some day be achieved which can be relied on to prevent complications and not to produce serum sickness. But until this is accomplished, many difficulties will have to be overcome and much more will have to be learned about the nature of scarlet fever pathology.

It is necessary to speak of one more measure, namely, the transfusion of blood from convalescent donors.<sup>22</sup> This has been used successfully in very severe cases on admission to the hospital, especially in those septic cases which do not yield to antitoxin and convalescent serum. Schultz<sup>23</sup> reports a case which did not respond to a full dose of antitoxin but the next day was greatly helped by a 300 cc transfusion from a convalescent scarlet fever donor. There are other factors in this transfused blood besides antibodies to counteract the toxin. Very large doses of convalescent scarlet fever serum have been used in a variety of streptococcic infections not of scarlet fever origin.<sup>24</sup> It would seem probable that the lucky strikes reported in some of these cases result from those other factors in the blood serum which are quite apart from and probably independent of scarlet fever antitoxin. The use of anti-streptococcic human sera for such cases selected on a titer basis would save convalescent scarlet fever serum for its more specific indications.

While the subject of patents hardly belongs under the head of progress in our knowledge of a disease, it is worthy of mention that the Dick patent covering the toxin and the antitoxin is controlled by the Scarlet Fever Committee in Chicago, through which licenses for manufacture and distribution are granted. The Dochez N. Y. 5, as well as all other strains derived from scarlet fever, appears to be embraced by the wording of this patent. The Dochez antitoxin patent is held by the Presbyterian Hospital in New York City. One lawsuit has resulted already over these products, and an unwholesome atmosphere has been created of which the practitioner and bacteriologist are conscious. The Dicks' discovery remains a monumental achievement in



[which] is dependent on the bone structure of the tympanic and mastoid areas and on whether or not the original lesion attacks the epitympanic space" In some cases mastoid destruction goes on very rapidly and operative delay is dangerous An ear which suppurates profusely for three weeks should be regarded as probably due to a mastoid abscess regardless of fever or mastoid tenderness An x-ray is of great value here Operation in these cases saves the hearing, sometimes life, and shortens the period of quarantine Removal of the tonsils and adenoids may be accomplished during scarlet fever with less danger than is commonly supposed, and often with decided benefit to the patient

*Sinusitis* may occur with the prodromal symptoms of scarlet fever or at any time in the course of the disease<sup>30</sup> Early surgical interference is to be avoided Empyema of the ethmoid sinus may penetrate the orbit and produce redness and edema of the upper lid and push out the eyeball This condition sometimes subsides of itself, but even in the severe forms, under skillful surgical care the prognosis is good A frontal sinus abscess may burrow into the subdural space in rare instances

*Nephritis* in a mild degree is a frequent accompaniment of the eruptive stage Acute glomerulonephritis, especially of the hemorrhagic type, varies in different epidemics from below 1 to above 12 per cent It occurs most frequently during the third week in an abrupt manner, and uremia may come on without previous warning in the urine or in the chemical analysis of the blood<sup>31</sup> Chilling seems to be responsible in a few cases<sup>32</sup> It was formerly thought that a milk diet prevented nephritis It is now recognized that the incidence is slightly greater if too much milk is supplied Nor is it the protein content of the milk which is now accused but the fat, which is thought to impair hepatic function and indirectly favor renal inflammation<sup>33</sup> Jurgens<sup>34</sup> suggests that potato be avoided because of the potassium content, but the facts are entirely against such an assumption A mixed diet suited to the age and the presence of fever is all that is required Milk should not be taken in excess

Thenébe<sup>34</sup> and his coworkers classify glomerulonephritis as "allergic manifestations" The question immediately arises

as to whether the toxin is allergenic Hooker<sup>36</sup> informs us that the purified toxin is not known to have allergenic properties, it has not been shown to sensitize the skin Streptococcal nucleoprotein, on the other hand, has this property Shall we assume, then, that the initial lesion is a kidney infection? Duval and Hibbard<sup>37</sup> in their animal experiments come to the conclusion that the glomeruli are first affected by the toxin, while the interstitial lesions result from infection These conclusions, however, are based on animal experiments, and there is no ground for assuming that free toxin in any appreciable amount exists in the third week of convalescence It is necessary to mention all these ideas in order to show what we do not know about nephritis When we realize this, we can proceed to treat the nephritis in the usual and accepted manner

*Endocarditis* (rare) \* Place<sup>38</sup> describes the characteristic heart damage as a benign endocarditis In recent years he has found this condition in less than 0.1 per cent of his scarlet fever cases, though formerly as high as 0.5 per cent. The diagnosis is based on the usual findings of fever, cardiac murmurs with tachycardia, and changes in the size of the heart, arthritis being a usual accompaniment He found that it usually appeared in the second or third week, persisted a few weeks, and subsided without further damage A murmur during diastole, or a murmur replacing a heart sound, or persisting through systole, he considers to be indicative of structural change While he recognizes that the crippling effect varies as in other forms of endocarditis, he is of the opinion that it is slight as compared with rheumatic fever

This brings up the point mentioned by White,<sup>40</sup> that it is difficult to determine to what extent scarlet fever is a cause of chronic valvular heart disease, because acute polyarthritis, "apparently rheumatic fever," occurs in about one-half of the scarlet fever cases where endocarditis or pericarditis develop

Salinger and Leonard<sup>41</sup> refer to the endocarditis of "allergic" origin, but the term is not generally accepted Stolte,<sup>42</sup> on the other hand, gives us a very practical classification of scarlet fever heart conditions The first group comprises those

\* Zischinsky<sup>39</sup> found only 10 among 20,000 hospital cases of scarlet fever in Vienna

benign conditions which Place has described, the second, those with arthritis, pericarditis, and the sweating so characteristic of rheumatic fever, the third, malignant endocarditis. In the first group, rest in bed is, of course, essential, but no medicinal treatment is indicated. Salicylates are helpful in the second group. Transfusions may be tried in the malignant type. The usual indications for digitalis are rarely present in the acute stage, and when they are present, pericarditis or septicemia is apt to interfere with any good that may be accomplished.

*Purpura hemorrhagica* (rare) may occur in a mild form early, but in its severe, abrupt, and fulminating form appears about the fourteenth day. The purpura may appear only on the lower part of the legs or arms. Again, it may suddenly involve the entire cutaneous surface and the mucous membranes, with a fatal outcome within forty-eight hours of its onset. Like acute glomerulonephritis, it appears to have no relation to the severity of the initial scarlet fever rash. Furthermore, it bears no relation to a previous history or family history of a purpuric diathesis.<sup>48</sup> Box<sup>43</sup> considers this complication to be due to a supersensitive stage in the course of establishing immunity. We might well speculate on its origin from the results of endothelial cell damage in the eruptive stage. In severe cases transfusion is indicated, and a convalescent scarlet fever donor may be used.

*Appendicitis* (rare) When this occurs in scarlet fever it is apt to be of the abrupt and fulminating type. Any delay in calling in surgical aid may result in rupture and peritonitis. If the appendix has not ruptured, a drain should not be used, as the wound will then surely slough wide open later. The wound should be closed tight, as in any clean case, even if the rash is in full bloom. There is a strong tendency for clean wounds, such as in a hernia operation, to slough wide open if scarlet fever supervenes on the operation. We have found that closing tight an unruptured appendectomy wound affords a very good chance of primary healing. It should be the duty of the attending physician to bring this forcibly to the attention of the surgeon called in.

*Empyema* (rare) When this develops in the course of scarlet fever, the closed method, even in adults, has been

found to be the safest initial surgical procedure, even though it sometimes has to be followed by a rib resection. One or moreappings may be advisable to favor the walling off process. Allowing a large amount of serum to accumulate is to be avoided. The determination of the presence of empyema in scarlet fever does not demand the haste of surgical intervention as in appendicitis.

The initial responsibility in all these surgical complications rests with the attending physician. He must learn to recognize their importance, and through his knowledge of scarlet fever he should continue to be an active adviser to the surgeon throughout the case.

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## DIPHTHERIA

### SERUM THERAPY IN MILD AND MALIGNANT DIPHTHERIA

Recent advances in our knowledge regarding the serum treatment of diphtheria deal with the size of the dose and the methods of administration. The prevalence of the malignant type of the disease in Austria, Germany, Scandinavia and England has stimulated a lively interest in this subject. These malignant cases occur sporadically in America, and their relatively poor response to vigorous antitoxin therapy has caused consternation abroad even to the point of downright skepticism as regards the value of this agent. To my mind, this attitude is wrong. Recognition of the possibility of the severe type should prompt us to avoid any unnecessary delay in treatment, instead of permitting us to adopt the nihilism emanating from Vienna (Zischinsky)<sup>1</sup>

The mechanism of antitoxin therapy is essentially a protective or preventive one. If the clinician grasps the fact that the curative virtue of antitoxin is based on its protective value, he will not allow himself to become confused by the recent unfavorable reports of antitoxin therapy in this disease, or by the divergent opinions regarding dosage and methods of administration.

Let us start with the undeniable fact that antitoxin is as capable of neutralizing the toxin as water is capable of putting out a fire. The basis for this statement lies in the very method by which a unit of antitoxin is standardized. But here we are immediately confronted by the statement of Friedberger<sup>2</sup> that the natural diphtheria in man is as different from the toxin diphtheria in the guinea pig as a man is from a guinea-pig. We admit the logic of this only to a certain extent. We are well aware that barriers of resistance exist in the mucous membranes of the upper respiratory tract of man which delay invasion and tend to prevent absorption of the toxin. These barriers, however, which vary so greatly in different individuals, may actually augment the danger because they are the cause of delays in recognition of the disease. This may

sound paradoxical, but it is not. A smouldering fire is potentially capable of bursting into flame. Diphtheria may smoulder, so to speak, and go out of itself, or it may take on a malignant aspect at the very start or after a period in which these barriers have tended to hold back the disease process. The amount of antitoxin necessary to neutralize the toxin in a given case depends on whether the process is being held at bay, and on whether a malignant aspect is manifest, and if so, how far it has proceeded.

In neutralizing the toxin in the guinea-pig, the antitoxin is usually given simultaneously. A dose which will save a guinea-pig if administered within fifteen minutes of the toxin will not suffice if given later. In fact, if we wait two hours and a quarter, a dose one thousand times as great will not suffice to save the animal<sup>3</sup>. When we realize that 1000 units of antitoxin to a guinea-pig corresponds to 100,000 units for a 50-pound child, we can easily understand why enormous doses of antitoxin so often fail to save malignant cases. The appreciation of these facts shows the difference as well as the relationship of experimental toxin diphtheria in the guinea-pig and the natural disease in man. It emphasizes the important part that time plays in the protective action of antitoxin.

It thus becomes obvious that the time element in conjunction with the stage of the disease process constitutes the basis for gauging the dose of antitoxin. Furthermore, we must bear in mind that antitoxin therapy is essentially protective. It does not dissolve the membrane. It does not destroy the bacilli. What it does is to neutralize the toxin, and thus, by protecting the tissues, it allows the operation of those other natural forces of the tissues, so vitally concerned with the recovery of the patient.

With these facts in mind we can understand why the question of the required dosage in cases of diphtheria cannot be met with definite answers. You might as well ask the chief of the fire department how much water on the average he needs to put out a fire. You know perfectly well that a pail of water will be enough at the start, but once it gets under way the answer becomes involved. If the house burns down, one does not say that water doesn't put out fire. This may

all seem so elementary as to appear entirely unnecessary. But when clinicians in posts of authority are voicing their disbelief in antitoxin as a result of their experiences with malignant diphtheria, it is time to revert to first principles.

Dosage, then, is dependent on the time element. It also depends on the manner of administration. The intravenous route gives us the most prompt action, but two-thirds of the antitoxin so given leaves the blood within twenty-four hours.<sup>4</sup> Thus, if conditions warrant this method of approach, it is desirable to inject another dose into the gluteus muscle, from which site it will be continually given off, reaching its maximum concentration in the blood at the end of twenty-four hours. The subcutaneous route is the slowest.

Park<sup>5</sup> in New York advocates a scale of dosage which varies from 3000 to 60,000 units. In Boston we have been accustomed to employ approximately twice as much. Recent accounts from Paris,<sup>6</sup> where the intramuscular and subcutaneous routes are used, advocate a scale running from 45,000 to 300,000 units. Bie<sup>7</sup> in Copenhagen has given as much as 500,000 units. Bie influenced many of us by his high scale of dosage, which was accompanied by an extraordinarily low death rate, but this was before the wave of malignant cases, which, in spite of this high dosage, has brought about a high death rate.<sup>8</sup> In Stockholm a high dosage scale was carried out from 1925 to 1928, but on analyzing the results Lichtenstein<sup>9</sup> found that the mortality in the severe uncomplicated faucial type remained the same as it had been over a previous period with much smaller doses.

From these hospital statistics we are confronted with the fact that the routine use of the larger doses shows no apparent advantage as determined by the yearly mortality and the incidence of postdiphtheritic paralysis. In other words, our attempts to protect well advanced severe cases have perhaps carried us beyond the maximal dose which could be effective. We must not lose sight of the fact that hospital mortalities are dependent on the promptness with which outside physicians recognize diphtheria. This applies not only to the above-mentioned smouldering type, but more particularly to the malignant type, where the time element becomes such a crucial factor.

From the point of view of the clinician the malignant type offers no new problem. It has been constantly with us in the sporadic form. Its increase would appear to result from unknown environmental conditions affecting man's resistance. It is not a new disease but a virulent form of the same one, occurring in parts of Europe as 10 per cent of the diphtheria cases. In Berlin the death rate in this type has been as high as 50 per cent.<sup>8</sup> Bacteriologically it represents a virulent strain with increased penetrating and increased toxin-producing properties. So fulminating is it at its worst that large doses given during the first twenty-four hours have proved ineffective. I have seen one case referred to us by one of my former interns who gave all the available antitoxin (30,000 units) before sending it to the hospital, where the child received 130,000 more units but died within thirty-six hours of the onset. No one was to blame. Antitoxin was simply ineffective because it could not protect against this overwhelming infection. To say that the antitoxin was ineffective as a protection by no means implies that it was inert. Animal experiments with these new strains give unsatisfactory results because animals may react more unfavorably to the milder strains than to the malignant strains.<sup>10</sup> To suggest that malignant types are due to mixed infections with a streptococcus<sup>4</sup> is to sidestep the issue. The streptococcus is found also in the blood of malignant smallpox cases. Where antistreptococcic sera have been used in conjunction with antitoxin the mortality was 55 per cent.<sup>8</sup> It is true that a mixture of scarlet fever and diphtheria was an ugly combination before the days of antitoxin, but it is no longer so formidable. If an antitoxin derived from a malignant strain<sup>11</sup> proves more effective clinically in these cases, we shall still be confronted with the time element of its administration. Since the regular antitoxin is capable of neutralizing the toxin of the malignant strains, every effort should be used to apply it early. In these cases it does not depend on the day of the disease but on the hour.

Another factor which has come to light in recent literature tends to bring us back to first principles, and also suggests that we may be overstepping the mark in dosage. In 1918 Bingel<sup>12</sup> gave us a surprise when he found that cases

treated with "normal" horse serum did as well as those given equal doses of antitoxin. He later informed us that the "normal" serum was obtained from horses used for antitoxin purposes in which the antitoxin titer had fallen to a very low level. Recently Hottinger and Toepfer<sup>8</sup> have concluded that they have reduced the mortality of malignant cases in their hospital in Dusseldorf from 43.5 per cent to 17.0 per cent (not including those moribund on admission) by giving 4000 units intravenously and repeating this dose intramuscularly two to four times a day with interspersed doses of this low titer antitoxin. Naturally, the idea of nonspecific protein therapy was brought forward as an explanation of these results. It has remained for von Bormann<sup>9</sup> to establish the fact that nonspecific protein therapy is not concerned with the results recorded by Bingel, Hottinger and Toepfer. By injecting various strains of diphtheria bacilli into the conjunctival sacs of guinea pigs he has tested the relative efficacy of these three sera. With antitoxin the animal is saved, and sometimes the eye is not damaged. With low titer antitoxin the animal is sometimes saved, but the eye is lost. With really normal horse serum there is a 100 per cent mortality. Over 300 animals were used. Since the guinea pig may be protected by serum with a very low antitoxin content, he argues that the use of the original method of giving 1000 to 2000 units in mild cases—doses with which antitoxin won its first laurels—is not so far wrong as we have come to think.

In other words, recent laboratory and clinical results suggest that the mild cases may be sufficiently protected by doses of 500 to 1000 units, that malignant cases, if treated early, may often be protected by frequently repeated doses of 4000 units, and that a certain number of malignant cases reach us too late to be saved from a fatal outcome by any amount of antitoxin. With this in mind, one is inclined to play safe by allowing plenty of margin in the milder cases and to persevere vigorously in the malignant ones with the hope that treatment may have been begun in time.

Thus the practitioners whom we were wont to accuse of giving inadequate doses may derive some satisfaction from the new light on this subject, while others like myself are prompted to recede cautiously from the maximal doses we

have been in the habit of using The theory that one large enough single dose at the beginning should be our aim, as advocated by Park and Schick, still applies to the mild types, and Park's dosage scale appears to be vindicated The frequent repetition of small or moderate doses in malignant cases would seem to be worthy of trial Roughly speaking, the minimal dose is 3000 units subcutaneously The maximal dosage is 500,000 units given intravenously and intramuscularly in repeated daily doses averaging 100,000 units While any scale of dosage is unsatisfactory because it is incomplete, the following is a rough guide to be varied by the duration of the symptoms and their severity

DOSAGE OF ANTITOXIN IN UNITS

| Weight of patient | Mild   | Moderate | Malignant. |
|-------------------|--------|----------|------------|
| Under 50 lbs      | 5,000  | 10,000   | 50,000     |
| Over 50 lbs       | 10,000 | 20,000   | 100 000    |

Antitoxin should not be used in the postdiphtheritic paralyses, first, because it does no good, second, because there is ample antitoxin in blood at this stage, and third, because of the danger of anaphylactic shock eight to nine days after the first dose

While the protection which antitoxin affords to man is not to be compared to the protection afforded by active immunization, we must keep in mind that the early bedside recognition of diphtheria governs the amount of antitoxin required

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### SOME RECENT ADVANCES IN VACCINES AND SERUMS A REVIEW

#### INTRODUCTION

It is manifestly impossible in this communication to discuss completely all the topics which this title might suggest. It seems wiser, therefore, to limit this review to those topics which are relatively new and which are receiving considerable attention from the medical profession at the present time. The writer intends to express freely his own opinions of the relative merits of these several biological products. The topics which will be reviewed are (a) whooping cough vaccine, (b) placental extract, (c) tetanus toxoid, (d) meningococcus antitoxin (Ferry), (e) staphylococcus toxoid, and (f) staphylococcus antitoxin.

#### WHOOPIING COUGH VACCINE

During the past few years two new products have received considerable attention for the prophylaxis of whooping cough. Furthermore, a few papers have appeared in recent years suggesting that a filtrable virus plays an etiological rôle in the disease. Since the etiological rôle of an organism in any disease should be definitely established before it is justifiable to use that organism in a prophylactic vaccine it will be well briefly to review the etiology of whooping cough.

Ever since *hemophilus pertussis* was first described by Bordet and Gengou<sup>1</sup> as the causative agent of whooping cough, occasional reports have appeared purporting to cast doubt on

the etiological rôle of this bacterium and suggesting that a virus may be a factor in the cause of the disease. The various arguments in favor of the virus theory have recently been summarized by Rich<sup>2</sup> as follows: (a) pertussis bronchopneumonia is an interstitial reaction, with mononuclear cells predominating, which is the characteristic type of histopathological response to virus infection, (b) pertussis results in a permanent immunity as in most virus diseases, whereas most bacterial diseases do not (Note: we might point out that several virus diseases are characterized by a very short immunity, *e. g.*, herpes labialis, the common cold, and influenza, and that prolonged immunity is supposed to follow some bacterial infections such as typhoid, cholera, plague, etc.), (c) *Hemophilus pertussis* is isolated only during the early stages of the disease, (d) intranuclear inclusion bodies have been described as occurring in the lungs of children dying of pertussis bronchopneumonia, (e) experimental transmission of the disease (Rich, 1932) has not been adequately demonstrated and thus Koch's postulates are not fulfilled.

Recently, Sprunt, Martin and Williams<sup>3, 4</sup> have answered the argument of Rich that the mononuclear interstitial reaction in the lungs suggests a virus etiology. These investigators produced this type of reaction in the lungs of rabbits by the intratracheal injection of pure cultures of Bordet-Gengou bacilli. A similar bronchopneumonia was produced with the typhoid bacillus. Furthermore, the same type of reaction was produced by the intratracheal injection of various bacterial toxins (*staphylococcus aureus*, hemolytic streptococcus and diphtheria toxins). These authors found that these reactions could not be differentiated from that occurring in children dying of pertussis bronchopneumonia or from that caused in animals by the viruses of epidemic influenza and psittacosis.

Within the past few years McCordock,<sup>5</sup> Rich<sup>2</sup> and McCordock and Smith<sup>6</sup> have demonstrated intranuclear inclusion bodies in the lungs of children dying of pertussis, which they feel suggests the possibility that a virus may be the primary etiological agent. Rich does suggest that these inclusion bodies might be due to aspirated herpes virus. McCordock also reviews a few instances from the literature where similar

bodies were found in nonpertussis patients. Furthermore, the inclusion bodies described by Farber and Wolbach<sup>7</sup> as occurring in the salivary glands of a considerable percentage of infants dying from a variety of causes are morphologically indistinguishable from the inclusion bodies described by the above authors in the lungs of patients with pertussis.

Because of these suggestions that a virus may play a rôle in the etiology of whooping cough some recent transmission experiments have been done which, in our opinion, offer very conclusive proof that *Hemophilus pertussis* is the sole etiological agent in this disease. It should be pointed out that with regard to the old transmission experiments cited by Rich<sup>2</sup> the dissociation of *Hemophilus pertussis* was not understood at the time when these investigations were done; it is likely that some of these experiments were carried out with avirulent strains.

Sauer<sup>8</sup> inoculated (into the nose and throat) healthy young Rhesus and Ringtail monkeys with virulent Phase I culture. In 8 out of 76 instances the animals developed a paroxysmal cough followed by vomiting of mucus after an incubation period of seven to twenty days. The organism recovered from one coughing animal produced the disease in another animal inoculated with it. This, of course, is not an entirely convincing experiment because of the very small percentage of positive results. In 1933, Macdonald and Macdonald reported a unique experiment on human volunteers. Four healthy boys whose medical histories were accurately known were used in these observations. Two of the boys had been vaccinated two months previously with the Sauer vaccine. The other two were nonimmune. The throats of all four were sprayed with the filtrate of the first generation of a freshly isolated culture. No symptoms developed. The boys were kept rigidly quarantined in a country camp. Eighteen days later a suspension containing 140 bacilli was dropped into the nose and throat of each boy. The nonimmune boys developed typical whooping cough with positive cough plates. The vaccinated boys remained free of symptoms and had negative cough plates even though they were all kept together throughout the period of observation. These authors conclude that the Bordet Gengou bacillus is the sole cause of whoop-

cough and that active immunity is conferred by the injection of *Hemophilus pertussis* vaccine

In Shibley's<sup>10</sup> more recent transmission experiment the virus possibility was examined still further. This author carried a Phase I culture through 60 generations in order to be certain that a virus was not carried over in the culture. With this culture he succeeded in producing a typical train of symptoms in a chimpanzee. The animal was sacrificed and *Hemophilus pertussis* was recovered from various locations in the respiratory tract.

We have not reviewed the additional positive evidence pointing to *Hemophilus pertussis* as the sole etiological agent of whooping cough. We merely desired to point out the inadequacy of the virus theory of etiology. In our opinion the evidence points conclusively to *Hemophilus pertussis* as the sole cause of the disease.

Within the past few years there has been considerable advance in our knowledge of the biology and antigenic composition of the Bordet-Gengou bacillus which has an extremely important bearing on prophylaxis by vaccination. Lawson<sup>11</sup> and Leslie and Gardner<sup>12</sup> have shown that *Hemophilus pertussis* is capable of undergoing dissociation into serologically different variants, which have been termed Phases I, II, III and IV. Each of these phases probably possesses a different antigenic structure. The serological differences between these mutation forms probably accounts for the several types of pertussis bacilli described in the older literature. As far as we know now *Hemophilus pertussis* is a homogeneous species. Phase I is always hemolytic and is the form recovered in the disease. It is the virulent phase and corresponds to the "smooth" form in general dissociation nomenclature. Phases III and IV are "rough" or avirulent. The importance of this is that if any prophylactic vaccine is to be of value it must be made from Phase I cultures.

Innumerable attempts have been made in the past to actively immunize children with *hemophilus pertussis* vaccines. Such attempts have been almost uniformly unsuccessful. Even Madsen's<sup>13</sup> unique experiences in the Faroe Islands are not entirely convincing. It is of some interest that in 1931 the Council on Pharmacy and Chemistry of the American

Medical Association removed pertussis vaccines from New and Nonofficial Remedies because there was no convincing evidence as to their value either prophylactically or therapeutically. In light of our present knowledge there are several possible reasons for the failure of these vaccines. Many of such vaccines were probably made from dissociated, avirulent cultures. Immunization generally was not done a sufficiently long time before exposure (in fact, in most instances such vaccines were administered either after exposure or during the early stages of the disease). Also the immunizing doses used were probably entirely too small.

In a series of communications during the past few years, Sauer<sup>14 16 18, 17</sup> has described his experiences with his new type of whooping cough vaccine. His vaccine is prepared and administered in such a manner that the probable reasons for failure of the older vaccines are overcome.

Sauer's method of preparing and administering his vaccine is as follows. We quote excerpts from his papers directly: "Bacillus pertussis vaccine (1 cc. = 10 billion bacilli), is made from recently isolated, strongly hemolytic (Phase I) strains, grown on Bordet (potato-glycerin extract agar) medium made with freshly defibrinated human blood. To minimize the culture medium content, the forty eight hour growth is scraped off and mixed with 0.5 per cent phenolized physiologic solution of sodium chloride. To insure purity, a stained smear of each surface growth is examined before it is harvested. After a week in the refrigerator (during which time it is shaken daily), the concentrated suspension is cultured for sterility on three successive days. After dilution with 0.5 per cent phenolized physiologic solution of sodium chloride so that 1 cc. contains about 10 billion bacilli, it is tubed, sealed and refrigerated until shortly before it is used."

Sauer has emphasized several essential points concerning the production of this vaccine which can be reiterated with profit. It should be made with freshly isolated, Phase I cultures. It is made with human blood medium because (a) the organism is more apt to be maintained in its virulent phase on this medium, (b) foreign blood protein from the medium cannot be taken up with the vaccine. This eliminates any possibility of sensitization and subsequent hypersensitive reaction.

We feel that it is probably not essential to use human blood. So far as we know the organism will maintain its original antigenic structure on sheep or other blood as well as on human blood. The vaccine is not heat killed, which eliminates any possibility of antigenic change or reduction of antigenic potency due to heat denaturation, etc.

A total of 8 cc or 80 billion bacilli are given in three bilateral injections at weekly intervals. They are given subcutaneously in the deltoid and triceps regions. Subsequent injections should not be given in the same spot as the preceding in order to avoid the possibility of a local reaction. Care should also be exercised that the injections are not given intravenously. The first injection consists of 1 cc in each arm, 1.5 cc being given in each arm at the second and third injections.

Sauer's experiences with reactions following these injections are as follows: "The local and systemic reactions are due to the vaccine (dead bacilli and endotoxin), and not to the phenol or medium proteins. Allergic reactions, sensitization to foreign protein and susceptibility to the Arthus phenomenon need not be feared, regardless of the amount of vaccine injected or the time interval between injections. If a severe reaction follows an injection, the next injection may be postponed a few days, or only 1 cc may be given (bilaterally) at subsequent injections and an extra one given a week after the third injection. The parents are forewarned of a transient rise in temperature, the temporary local reactions (redness, induration and tenderness) and the subcutaneous nodules, which may persist for a few weeks at the site of each injection."

Since the first three years of life constitute the danger period in whooping cough mortality, prophylactic vaccination should preferably be done during infancy. Sauer recommends that it be done during the second half of the first year of life. It would also be advisable to immunize older, nonimmune children who have some chronic or debilitating disease such as tuberculosis, asthma, chronic pulmonary suppuration, etc.

One extremely important point emphasized by Sauer is that whooping cough vaccine is of no value unless *it is given at least a month or longer before exposure. It is of no value*

*if given after exposure or during the catarrhal stage and is of no therapeutic value at any time during the course of the disease* This, of course, is in keeping with the general immunological principles governing active immunization in any acute disease.

Sauer has published very convincing evidence, obtained from well-controlled studies, as to the effectiveness of whooping cough vaccine. In one of his studies he was able to vaccinate certain children in individual families and leave the others as controls. During the course of five years 31 of such control children in 24 families developed whooping cough, whereas, 29 vaccinated children in these same families who were intimately exposed during the incubation, catarrhal and paroxysmal stages, failed to develop the disease. During the same period 162 vaccinated children who were accidentally exposed failed to develop the disease. We have already quoted, in our discussion on etiology, the experiences of Macdonald and Macdonald, which are excellent evidence for the effectiveness of prophylactic vaccination. Recently, Sauer<sup>18</sup> has described a few failures of his prophylactic vaccination.

During the past few years Krueger<sup>19 20 21</sup> and his associates have described their method for the production of a so-called "pertussis" undenatured endo-antigen. We quote freely the description of their method. Phase I organisms are harvested in buffered, isotonic solution, thoroughly washed to remove metabolites and then mechanically disrupted by grinding for twelve hours in a special type of ball mill. The resultant suspension is subjected to ultrafiltration through acetic collodion membranes of such porosity that all intact cells are retained while material in solution or in a finely dispersed phase passes through. The *water-clear* filtrate contains those constituents of the live cell put into solution or suspension by physical rupture of the cell membrane. Each cubic centimeter contains the extract from 12 billion organisms.

We feel that there is insufficient evidence available to justify the assumption that this is a better immunizing agent than the vaccine prepared of whole organisms according to Sauer's method. Grinding will undoubtedly produce a suspension of smaller particles, however, the bulk of substance will probably be in physical suspension rather than in true chemical



solution Under these circumstances the method of ultrafiltration which results in a "water-clear solution" will undoubtedly remove considerable immunizing substance Furthermore, the method makes it difficult to quantitate dosage in terms of the amount of original substance Recently an attempt has been made to standardize this product by nitrogen determinations Krueger's main claim is that his antigen is "undenatured" because it has not been heated We might point out again that Sauer's vaccine is *not heated*—in fact, it is subjected to much less physical manipulation than is Krueger's endo-antigen

Miller<sup>22</sup> has reported results in rabbits suggesting that Krueger's extract is better than other immunizing preparations He determined this by means of complement fixation which, in our opinion, is not especially reliable for a quantitative study of the development of active immunity Rabbits are poor animals for the study of such a problem since they are not susceptible to *Hemophilus pertussis* infection, or rather, they are naturally immune to it

Frawley and his associates,<sup>23</sup> Stallings and Nichols,<sup>24</sup> and Munns and Aldrich<sup>25</sup> have reported results on the therapeutic use of Krueger's antigen in which they claim definite benefit from it They do not seem to us to have proved this claim In view of Sauer's experience that whooping cough vaccine is of no value in treating the disease (and this is the experience in other well-controlled observations) we see no reason why Krueger's antigen should have any therapeutic value at least insofar as such therapeutic value is dependent upon the development of an active immunity Frawley<sup>26</sup> used this antigen prophylactically, and found that he did not get complete protection, although he states that the disease was milder This experience, it seems to us, is further proof that this antigen is of no therapeutic value when given during the course of the disease It is always difficult to appraise, even after careful questioning, the statements of a solicitous mother regarding the effect on her child of an "injection for his whooping cough" We feel that there is no justification for the use of any pertussis antigen or vaccine as a *therapeutic* agent

In summary, it seems to us the evidence so far advanced indicates that whooping cough vaccine, as Sauer has prepared



300 cc of the salt solution was added for each placenta. The material was stirred mechanically for half an hour, and at the end of this time the tissue debris was removed by filtration through cheesecloth after which the blood cells were removed by centrifugation. Extraction of each lot was repeated once or twice so that the total amount of saline used was from 750 to 1000 cc per placenta.

"Such extracts contained fetal blood, some maternal blood, and a quantity of placental tissue protein. Because of the association of immune bodies with the globulins of the blood serum of lower animals and presumably of human beings a concentrate of the active material and the removal of inert or noxious matter was sought by separation of the globulin fractions through precipitation with ammonium sulphate. Tests for toxicity and sex hormones indicated that the globulins contained a negligible amount of the hormones and that they were nontoxic for animals even if injected in large doses. Also, by animal tests and clinical trial the antibodies sought were found to be present in the globulin fractions."

Further differential precipitations were carried out at different concentrations of ammonium sulphate. The ammonium sulphate was removed by dialyzing in cellophane tubes against running water and isotonic salt solution. The material was preserved and sterilized by adding merthiolate 1:5000 or by passage through a Berkefeld filter.

In general it has been found that placental extracts are capable of (1) neutralizing diphtheria toxin, (2) blanching a scarlet fever rash, (3) neutralizing poliomyelitis virus, and (4) preventing or modifying measles.

In their most recent paper McKhann, Green and Coady have presented the results obtained by studying the several protein fractions of placental extract as well as the total result of their experiences in the prevention and modification of measles with these substances. It was found that the substance neutralizing diphtheria toxin was found almost entirely in the pseudoglobulin fraction. The substance responsible for blanching scarlet fever rashes was also found almost exclusively in this same fraction. It was shown that injections of placental extract subcutaneously or intramuscularly in patients with a positive Dick reaction were followed by a period of

several days during which Dick tests were negative. This same observation was made independently by Ross<sup>81</sup>

This striking protein distribution was not present in the case of antibodies for virus diseases, that is, for measles and poliomyelitis. In these instances the antibodies were distributed about equally between three fractions, the pseudoglobulin, the euglobulin and the tissue proteins.

These authors have presented data describing the use of placental extract for the prevention or modification of measles in 1285 nonimmune children. The several protein fractions were used. In one group of 560 children who were intimately exposed (under circumstances such that one would expect an infection rate of some 90 per cent) measles was either modified or prevented in 93 per cent.

With regard to reactions following the injection of placental extract in this large group of patients it was found "that 23 per cent of the patients had mild local reactions and that 12 per cent had a slight general reaction as indicated by fever. The incidence of severe local reactions was 2.8 per cent and of more severe febrile reactions (indicated by an elevation of temperature over 101° F), 1.9 per cent. In no instance did a local reaction persist longer than four days, and in no instance did suppuration occur." Reactions were more frequent among older children and adults than among infants and young children. Placental extract was found not to sensitize patients to subsequent injections of this material.

There appears to be no question but that placental extract is capable of preventing or modifying measles and should, therefore, be a valuable agent in the control of this disease. There is no reason to suppose that the activity of placental extract is due to substances different from those contained in convalescent serum. Its greatest merit would seem to be that an adequate supply of the material can always be available. It should do away with the trouble and annoyance of seeking and obtaining convalescent serum at just the right moment when occasion for its use arises.

As McKhann has pointed out, the immunity conferred by an injection of placental extract is passive and therefore of short duration. For this reason it is probably best not to use it for protection except in institutions and in debilitated,

tuberculous, acutely or chronically ill children Its greatest value should be in its use as an agent to cause modified or mild measles It is probable that under these circumstances permanent immunity against measles would result McKhann has also pointed out that it is necessary to improve the product further to remove substances which might cause reactions and that some method of more certain and uniform standardization is very desirable In the use of this extract it is most important that potent products, so prepared as to lessen the possibility of reactions, should be obtained

### TETANUS TOXOID

During the past few years tetanus toxoid has been developed and this product bids fair to supplant the older methods of prophylaxis against tetanus infection

In 1924 and 1925 Ramon<sup>32 33 34</sup> published his classical studies on rendering diphtheria toxin nontoxic by treating it for several weeks at 37° C with 0.4 per cent formaldehyde At about the same time Descomby<sup>35</sup> found that tetanus toxin could be rendered nontoxic by treating it in the same way This product, toxoid, retained its antigenic properties in spite of the loss of toxicity, and thus offered a method for active immunization against tetanus

Tetanus toxoid is prepared by the addition of 0.3 to 0.4 per cent formaldehyde to tetanus toxin and incubating the mixture at 37° C for several weeks The end-point of the period of incubation is determined by the loss of toxicity of the material for laboratory animals By such treatment a toxin with an MLD of 0.001 to 0.0001 cc can be so reduced in toxicity that 10 cc will fail to kill a guinea pig Such toxins are considered to be adequately changed to toxoid when 5 cc to 10 cc fail to cause symptoms of tetanus when injected into a guinea pig Bergey<sup>36</sup> and others have shown that the best toxoid is derived from the most potent original toxin

There have been a number of studies on the production of antitoxin in human beings and animals following two or three injections of toxoid at biweekly or triweekly intervals Such studies have been published by Ramon and Zoeller,<sup>37, 38</sup> Sacquépée,<sup>39</sup> Lincoln and Greenwald,<sup>40</sup> Sneath,<sup>41 42, 43</sup> Bergey

and Etris<sup>44</sup> <sup>4</sup> <sup>46</sup> and Bergey<sup>36</sup> Ramon<sup>47</sup> has recently published a review of this entire subject. In general these studies have shown that the rise in antitoxin following the primary stimulus is rather slow, reaching a maximum in from three to five months. After this interval of time in persons receiving two or three injections of toxoid the antitoxin level in the serum averages about that occasioned by the injection of the usual prophylactic dose of antitoxin. However, in a large group of immunized individuals, there will be considerable variation in the level of antitoxin in their serum. This immunity apparently lasts for a considerable period of time. The serum antitoxin level apparently maintains itself for twelve to eighteen months and then slowly begins to fall. Ramon and Zoeller<sup>48</sup> injected a large group of individuals with tetanus toxoid and in some of them the serum antitoxin level following this varied from 0.5 to 1 unit per cc. Four years later 12 of these individuals had serum antitoxin contents of from  $\frac{1}{1000}$  to  $\frac{1}{10}$  unit per cc.

It has also been shown that a secondary stimulus (an injection of toxoid in a person immunized some time previously) is followed by a very rapid rise in antitoxin to a new high level. Such a secondary stimulus is followed, in from seven to fifteen days, by a rise in antitoxin which may be several hundred times greater than the antitoxin level just prior to the secondary stimulus. In fact the level attained after such a stimulus is usually many times higher than the optimum level following the primary stimulus. The importance of this will be discussed later.

Recently, Bergey<sup>36</sup> has shown that tetanus toxoid can be precipitated with 2 per cent alum. When washed according to the method of Wells, Graham and Havens<sup>49</sup> this purified alum toxoid was not followed by the annoying reactions which sometimes followed the use of nonprecipitated toxoid. Because alum toxoid is retained longer in the tissues it acts as an antigenic stimulus for a much longer time than regular toxoid. A single dose of alum toxoid is followed by an antitoxin content similar to that following three injections of regular toxoid.

There is no question but that tetanus toxoid is an active immunizing agent and that it would seem to be perfectly

possible to immunize individuals against tetanus. However, it remains to be seen to what extent it will receive practical application. The incidence of the disease in the general population is sufficiently low to make it questionable whether large-scale immunization would be advisable. There is no question but that such immunization should be of great value in that portion of the population whose occupations make them special tetanus risks, *i. e.*, agriculturists and men engaged in animal husbandry and military campaigns.

In actively immunized individuals, even though the immunizing injections were given a considerable time previously, and their serum antitoxin may be very low at the moment, it should be possible to protect them against tetanus by administering another dose of toxoid at the time of an injury. We have already spoken of the rapid and marked rise in serum antitoxin following a secondary stimulus. Thus, when a previously immunized individual is injured he is given an injection of tetanus toxoid instead of tetanus antitoxin. Such a procedure, of course, avoids the development of serum sensitivity in such an individual. There will then be a sufficient rise in his own antitoxin level within the incubation period of the disease to protect him against tetanus. Furthermore, it is possible, in soldiers and others running a particular tetanus risk, to keep their serum antitoxin at an effective level at all times by giving a single injection of toxoid every twelve to eighteen months after they first have been immunized.

It should be pointed out and emphasized that tetanus toxoid is of no value as a therapeutic agent. It should never be given during the course of the disease. It is solely an active immunizing agent and should be used only for prophylaxis against the possible development of tetanus following a future injury. Furthermore, because of the slowness of antitoxin development following a primary stimulus it should never be used as a prophylactic agent at the time of an injury in a person who was not actively immunized previously.

It is regrettable that there is no simple test, analogous to the Shick and Dick tests, to determine susceptibility to tetanus. An estimation of the degree of protection in an individual can be determined only by measuring the amount of antitoxin in his serum. This is an elaborate procedure which





the resulting filtrate is said to contain an exotoxin. They have found that such filtrates contain a toxic substance specific for each of the four Gordon types of meningococcus and an additional toxic substance common to these four Gordon types.

These authors have shown that when their toxin is appropriately diluted in physiological salt solution it will, after its intracutaneous injection, cause a positive reaction, similar to the Dick reaction in a certain percentage of human beings. Individuals recovered from meningitis failed to give a positive skin reaction when injected intracutaneously with a toxin prepared from the same type of meningococcus as isolated from the patient. They claim that it was also possible to neutralize this reaction in susceptible individuals with the appropriate "antitoxin."

Ferry has immunized horses with his bouillon filtrates for the production of a meningococcus "antitoxin." The resulting serum has been used by him in a large number of animal protections and therapeutic experiments. Monkeys, rabbits and guinea pigs were used. Without reviewing in detail the numerous experimental protocols of this author, we may summarize by stating that Ferry has concluded from the data obtained that the meningococcus produces a soluble exotoxin and that a true antitoxin can be developed by immunization with this exotoxin.

In our opinion sufficient evidence has not been advanced to prove that the meningococcus produces a true, soluble exotoxin. It has long been known, of course, that the meningococcus produces a potent endotoxin. The reactions of this substance have been studied in great detail by Gordon<sup>56</sup> and by Murray<sup>57</sup>. Recently Malcolm and White<sup>58</sup> have published studies on meningococcus endotoxin. The reactions of animals to endotoxin, as described by Malcolm and White, are in no way different from those described by Ferry as being due to exotoxin.

The meningococcus is extremely susceptible to autolysis or self-digestion, which liberates intracellular toxic substances or endotoxin. This is particularly true when the organism is grown in a fluid medium. When the organism is grown in broth for four to six days there is abundant opportunity for the liberation of endotoxin by this autolytic process. There-

fore, immunization with such filtrates could result in the production of antiendotoxin. Such a serum need not be any different from the antibacterial sera produced by the usual methods of immunization with meningococci. We feel that Ferry's "antitoxin" is such a serum.

In Ferry's numerous protocols showing the protective and therapeutic effect of his "antitoxin" there is no evidence to show that it will neutralize in multiple proportions, which is a fundamental characteristic of true antitoxins. Furthermore, the effect of his serum, in the majority of instances, was studied in animals injected with living virulent meningococci, and there is no reason to believe that such effect was other than antibacterial. Furthermore, most laboratory animals, *i. e.*, rabbits and guinea pigs, are not truly susceptible to infection by the meningococcus.

An "antitoxin," moreover, could not be expected to rid the subarachnoid space of organisms, a result which is essential for cure of a patient with meningitis. No doubt such an antitoxin might relieve a patient of certain of his symptoms. On the other hand, there is no evidence that an antitoxin has any direct effect on bacterial cells. This has been abundantly demonstrated in the case of meningitis due to other organisms. For example, Dick antitoxin, regardless of the route of administration, does not alter the course of meningitis due to the scarlet fever variety of hemolytic streptococcus.

Hoyne<sup>60</sup> has recently published an analysis of a group of cases treated with Ferry's meningococcus "antitoxin." In this study 211 cases were treated with regular antimeningococcus serum and 85 cases were treated with "antitoxin." The mortality in the former group was 45.9 per cent, which is higher than that generally reported. The mortality in the antitoxin treated group was 23.5 per cent, which is about the usual mortality rate given by others<sup>60, 61, 62, 63</sup> for patients treated with regular antimeningococcus serum. Furthermore, this paper loses much of its statistical value because, as the author states, in 40 cases the clinical diagnosis was not verified by smear or cultures.

Banks,<sup>64</sup> in England, has used meningococcus antitoxin in a small series of cases. The mortality in this group was 28 per cent. He concludes that this mortality is no better than

the standard mortality rate given by Flexner for patients treated with regular antimeningococcus serum

In conclusion we are not trying to show that Ferry's "antitoxin" is without value. We have endeavored to point out that, in our opinion, it is not different from the usual antimeningococcus serum and there is no reason for using it in preference to such products. We do object to its being used on the assumption that it is a true meningococcus "antitoxin." The evidence is not sufficient to justify its being so considered.

#### STAPHYLOCOCCUS TOXIN, ANTITOXIN, AND TOXOID

Staphylococcus toxoid and antitoxin are of direct interest to the clinician as possible therapeutic agents in certain types of staphylococcus infections. Before they can be discussed, however, it is necessary to review the properties of staphylococcus toxin. Toxic properties of the filtrates of staphylococcus cultures were first observed in the early days of bacteriology. The modern development of the subject will be reviewed below. Acute interest in the entire staphylococcus problem was revived by the Bundaberg accident. In this unfortunate episode 21 children were inoculated with a diphtheria toxin-antitoxin mixture that was contaminated with staphylococcus aureus. Twelve of these children died of acute staphylococcus septicemia within twenty-four to forty-eight hours. However these children did not die of toxemia, but of an acute, fulminating staphylococcemia. This was shown by Burnet<sup>65</sup> and by the Report of the Royal Commission,<sup>66</sup> which investigated it. It was shown that the toxin-antitoxin was heavily contaminated with living staphylococcus aureus and that little, if any, soluble toxin was present in the mixture. Burnet<sup>65</sup> showed that the conditions under which diphtheria toxin-antitoxin mixtures were prepared and kept, even though contaminated by toxicogenic staphylococci, were unfavorable for the development of toxin. We mention this because a few recent students of the problem, in reviewing this occurrence, have implied that staphylococcus toxin was the important factor in the death of the children.

The toxic principles in filtrates of staphylococcus cultures manifest themselves, under experimental conditions, in several

ways The important manifestations are as follows (1) Hemolytic activity Potent filtrates, even in high dilution, will hemolyze a suspension of erythrocytes Rabbit cells are generally used for such purposes (2) Dermonecrotic activity Such filtrates, even when considerably diluted, will cause an area of erythema with marked central necrosis when injected intradermally into rabbits and other animals (3) Lethal effect Such filtrates kill animals with extreme rapidity when injected intravenously Rabbits die within one to three minutes following the injection of an appropriate dose Dolman<sup>67</sup> has found other animals, including the guinea pig, horse, cat, and mouse, to be susceptible and subject to this rapidly lethal effect. It should be pointed out that this is an unusual property for a bacterial poison Practically all other bacterial toxins require a definite incubation period of at least several hours before their action is apparent The lethal effect of staphylococcus filtrates appears to be due to a direct action on the A V bundle in the heart (4) Leukocidin effect. Potent staphylococcus filtrates have a destructive action on leukocytes The older literature concerning these properties of staphylococcus filtrates has been reviewed by a number of recent investigators, including Burnet,<sup>65</sup> Dolman<sup>67</sup> and Weld and Gunther<sup>68</sup>

That human beings are susceptible to the toxic principle in staphylococcus filtrates has been shown by a number of observations In attempting to immunize patients with subcutaneous injections of small doses of toxin, Weiss<sup>69</sup> noticed that six to twelve hours after such injections there was often local redness and tenderness and occasionally swelling He reported one instance where the injection of undiluted toxin was followed by intense inflammation and suppuration and with marked systemic symptoms Pilot and Afremow<sup>70</sup> showed that the intradermal injection of diluted toxin in man caused a zone of erythema with swelling and tenderness within 24 hours They were able to neutralize these reactions with immune horse and rabbit serum Stevens<sup>71</sup> reported 3 cases of acute staphylococcus aureus infection with a scarlatiniform rash It was difficult to distinguish the rash in these cases from that in scarlet fever The rash could be blanched with staphylococcus antitoxin

In discussing the properties of staphylococcus toxin, especially its effect on man, mention should be made of another substance produced by certain strains of staphylococci which causes an acute gastro-enteritis. This substance has been found responsible for a number of outbreaks of so-called "food poisoning." Such outbreaks have been described and others reviewed by Jordan<sup>72 73 74 75</sup> and his associates. As has been shown by Dolman,<sup>76</sup> this "gastro-enteritis" principle is different from the toxin responsible for the effects enumerated above.

The production of potent staphylococcus toxin is dependent upon growing the organism under special cultural conditions as has been shown by Parker,<sup>77</sup> Dolman,<sup>77</sup> Burnet,<sup>77</sup> Parish and Clark,<sup>78</sup> Bigger,<sup>79</sup> Bigger, Boland and O'Meara<sup>80</sup> and Leonard and Holm.<sup>81</sup> In general, the most potent toxins are obtained by growing the organism in a semisolid agar with a buffered broth or peptone base. Cultivation is carried out under an increased carbon dioxide tension. The amount of carbon dioxide used has varied from 10 to 80 per cent in the hands of different investigators. The toxin is easily destroyed in an alkaline reaction which makes it imperative to use a buffered medium. It is possible that the effect of carbon dioxide may depend entirely upon its buffering action. After forty-eight hours' incubation the inoculated semisolid agar mass is squeezed through cheesecloth. The resulting fluid is centrifuged and filtered through a Berkefeld candle. The reaction of the filtrate is adjusted to slightly acid, pH 6.8. Staphylococcus toxin is thermolabile, being destroyed by heating to 60° C for five minutes.

There is, apparently, no correlation between the invasiveness of a particular staphylococcus strain and its ability to produce a potent toxin. Stevens and Carp<sup>82</sup> studied 31 strains that were obtained from two sources. One group of strains was obtained from human lesions, such as furuncles, abscesses, and septicemias. The other group was obtained from the nasopharynx of normal individuals. The toxin produced by the various strains was apparently identical since the reaction of each toxin could be neutralized by the same antitoxic serum. There was no correlation between amounts and the properties of the toxins produced and the clinical origin of cultures.

With respect to the organisms isolated from acute infections there appeared to be no relationship between the severity of the infection and the ability of the corresponding strain to produce toxin

There is considerable discussion in the literature as to whether the hemolytic, lethal, and dermonecrotic effects of staphylococcal filtrates are due to three different substances or whether these are different effects of a single toxic substance. On the basis of adsorption experiments Weld and Gunther<sup>65</sup> concluded that these different effects were due to different substances in the filtrates. On the other hand, nearly all other investigators subscribe to the view that a single toxin is responsible. Dolman<sup>67</sup> found that heating at 60° C for different lengths of time caused the same relative effects on both the hemolytic and dermonecrotic titers. In studying the action of formalin on staphylococcus toxin Burnet<sup>63</sup> concluded that "all the characteristic activities of the toxin are lost concurrently in the process of formalin detoxication. In none of the experiments with partially detoxicated preparations has there appeared any indication that the three functions of the toxin, hemolytic, skin necrotic and lethal have been dissociated." Because there is practically complete agreement that the various manifestations of staphylococcus filtrates are due to a single toxin the Committee on Standards of the League of Nations<sup>64</sup> has provisionally adopted a method for standardizing staphylococcus antitoxin depending only on hemolytic activity. Separate assays dependent upon the dermonecrotic and lethal effects are not required.

All investigators are agreed that staphylococcus toxin is antigenic and that it is a true bacterial soluble exotoxin. The immunological reactions of this toxin and its antitoxin are, in general, the same as those which characterize true bacterial exotoxins as a class.

Staphylococcus toxin can be detoxified by formalin with great ease. After only a few hours' incubation in the presence of 0.3 per cent formaldehyde there is a marked reduction in its toxic action. After forty-eight hours' incubation it is practically completely atoxic. The toxoid is an effective immunizing agent.

Before reviewing the clinical use of staphylococcus toxoid

some consideration should be given to the question of natural antitoxin in man. This has been studied by a number of investigators, including Connor and McKie,<sup>85</sup> Ramon, Richon, and Descazeaux,<sup>86, 87</sup> Bryce and Burnet,<sup>88</sup> and Murray.<sup>90</sup> In general the presence of "natural" staphylococcus antitoxin in man is somewhat similar in its distribution to that of diphtheria antitoxin. According to Murray and to Bryce and Burnet, umbilical cord blood and the blood of newborn infants contains antitoxin in practically the same amounts as in the maternal blood. This is gradually lost during early infancy. In later years there is a gradual rise in antitoxin to what is assumed to be a "normal" level. Expressing his values in terms of International units Murray found an average value of 0.78 units per cc for the blood of newborn infants, 50 cases having been examined. In 50 pregnant women he found an average value of 0.75 units per cc. This investigator also found that the level of antitoxin in patients with chronic pyoderms of various kinds was not significantly different from his "normal" value. In 7 patients with osteomyelitis, however, the average value was 11.7 units per cc. Parish, O'Meara and Clark<sup>89</sup> report similar experiences.

During the past few years a number of investigators, particularly Parish, O'Meara and Clark,<sup>89</sup> Murray,<sup>90</sup> Ramon, Bocage, Richon and Mercier,<sup>91</sup> Dolman<sup>92, 93</sup> and Connor and McKie<sup>94</sup> have treated patients suffering from chronic staphylococcal infections with staphylococcus toxoid. Patients are usually given a series of subcutaneous injections at weekly intervals. The initial dose is small, *i. e.*, 0.05 to 0.1 cc and is gradually increased at each subsequent injection. A series has usually consisted of 4 to 6 injections. In many instances such a series of injections has been repeated one or more times. It has been found that in the majority of patients there has been a gradual rise in antitoxin level to many times the titer at the beginning of treatment. Murray has made the interesting observation that there appears to be an optimum level to which antitoxin will rise following the administration of toxoid. Further injections will not increase it. It is interesting to note that this level is quantitatively similar to that naturally present in patients with osteomyelitis. He suggests that measuring the antitoxic titer in patients'

sera provides a reliable index for stopping treatment. There is no purpose in administering additional toxoid when the level above referred to has been reached.

It is generally agreed that a majority of patients with chronic pyodermias such as recurrent furunculosis, pustular acne, recurrent styes, blepharitis, carbunculosis and other superficial abscesses and sycosis barbae are considerably improved by treatment with toxoid. A small percentage of patients are not helped. Kindel and Costello<sup>5</sup> were unable to observe favorable results in their patients. Their work has been criticized by Dolman on the ground that they used a toxoid produced by a single strain of staphylococcus rather than a pooled toxoid from several strains. We cannot agree with Dolman in this criticism. There is no evidence at the present time that there is more than one antigenic type of dermonecrotic toxin. For this reason there is no justification for using a pooled rather than a monovalent toxoid.

In reading the several reports concerning the clinical value of toxoid it is difficult to form an independent judgment concerning it. In most reports the cases have not been presented in a sufficiently objective manner to permit the reader to judge for himself. Murray's report is an exception. From his tables and the manner in which he studied his cases, it seems apparent that many of his patients with chronic skin infections were definitely benefited. It should always be remembered, of course, that it is very difficult to control the appraisal of the effectiveness of a therapeutic procedure in this type of infection. One can never know which crop of furuncles would have been the last in a given patient even if no treatment had been used.

With regard to osteomyelitis there is no convincing evidence that toxoid is of value. In this connection we might recall again Murray's observation that the antitoxin level in such patients is essentially equal to the optimum amount occasioned by a series of injections of toxoid.

In summary, it is our opinion that staphylococcus toxoid is a useful agent in the treatment of chronic staphylococcal skin infections. For this purpose a toxoid of known antigenic potency should be used. Injections should be given subcutaneously, starting with a relatively small dose,  $1 \text{ c.}, 0.05$



or 0.1 cc. The dose can be increased gradually at subsequent injections. One of two series of 4 to 6 doses each may be given. Five to seven days should elapse between injections. If results are not obtained after such a course of treatment there is no point in continuing it further. If possible, it is a good plan to determine the antihemolytic titer of patients' sera before and after such treatment.

In our opinion there is no convincing evidence at the moment that staphylococcus toxoid is of any value in infections other than the group of chronic pyoderms. In the present state of our knowledge we cannot advise its use in osteomyelitis and generalized pyemic infections. Furthermore, it definitely should not be used in acute and fulminating staphylococcal infections.

Considerable work has been done with staphylococcus antitoxin during the past few years, both in experimental animals and in human infections. Parker and Banzhaf<sup>90</sup> were among the first to produce in horses a staphylococcus antitoxin which was capable of neutralizing the dermonecrotic effect of the toxin. We are not aware of any reports of the use of this serum in human infections.

Burnet<sup>65</sup> in carefully controlled experiments in rabbits was unable to obtain convincing results in experimental infections with living organisms. When antitoxin was given intravenously immediately after an intravenous injection of living culture, the life of the animals was prolonged. This author was also able to demonstrate the production of staphylococcus toxin in vivo. In three rabbits dying acutely from staphylococcus septicemia the pericardial exudate contained a skin-reacting substance that could be neutralized by antitoxin. On the other hand, when rabbits were actively immunized by the subcutaneous injection of living cultures they failed to die acutely, but invariably died in from four to thirteen days from generalized pyemic infections. Parish and Clark<sup>78</sup> and Parish, O'Meara and Clark<sup>69</sup> found that life could be prolonged in rabbits passively immunized with antitoxin.

These experiments have considerable significance. They indicate that antitoxin may protect against acute death in staphylococcus septicemia and suggest that such acute deaths may be due to the in vivo production of toxin. However, it

does not protect against late death due to widespread pyemic lesions. This is to be expected, since the antitoxin has no bactericidal action whatever. Nor can antitoxin be expected to protect against the development of widespread pyemic lesions during the course of acute septicemia. A similar situation exists in other infections. For example, there is accumulating evidence that septic complications are not prevented in scarlet fever patients passively immunized with Dick antitoxin.

Several reports have appeared in which staphylococcus antitoxin was used in human infections. Pantou, Valentine and Dix<sup>97</sup> report favorable results following its use in a small group of patients. Jamieson and Powell<sup>98</sup> are less enthusiastic in their use of antitoxin. While they do not give details of the patients in which antitoxin was used, they summarize their experiences as follows: "In staphylococcus pyogenic infections it has appeared that staphylococcus antinecrotizing serum has produced no uniformly good results. Vigorous intravenous and intramuscular antitoxin treatment in such cases extending over periods of from one or two to thirty days has sometimes had a favorable effect in reducing temperature and preventing daily chills, but blood cultures have in the main continued to be positive during serum treatment and metastatic infections have not been decreased or prevented. Local applications of staphylococcus antitoxin to abscesses have had a favorable effect in some cases, however, the efficacy of such treatment has not exceeded that commonly reported in the use of bacterial lysates." It is of interest to note the similarity of these results in human beings to those discussed above in experimental animals.

Dolman<sup>99</sup> has reported a large series of various types of staphylococcus infections and is an enthusiastic advocate of this form of therapy. However, because of the manner in which he reports his cases, it is difficult for the reader to form an independent appraisal of the results. At least his condensed mortality table is not convincing. Many of his cases received enormous doses of serum.

In summary, our own opinion, regarding the use of staphylococcus antitoxin is that it may relieve certain symptoms and may, in some cases of acute septicemia, prevent early death.

On the other hand, there is little reason to suppose it to have much curative value in subacute or chronic pyemia and osteomyelitis. Indeed, it might be said that antitoxin might change an acute, fulminating septicemia into the chronic type of pyemia with continuing positive blood cultures and developing pyemic abscesses. In the latter type of disease there is little to be expected from antitoxin treatment on the basis of existing evidence. It should be emphasized again that this antitoxin has no demonstrable bactericidal effect. We, therefore, feel that the therapeutic usefulness of staphylococcus antitoxin is limited.

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## CLINIC OF DR. JOE VINCENT MElIGS

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### RECENT ADVANCES IN MEDICAL GYNECOLOGY

THE purpose of this paper is to cover the recent advances in gynecology that are of value to medical men particularly. It is quite impossible to exclude certain advances that are of greater importance to surgeons and gynecologists. The subjects to be discussed cannot include all the advances but are selected by the author as necessary for the proper practice of medicine. Gynecology is so closely allied to medicine, endocrinology, physiology, pathology, and surgery that real gynecological knowledge should be all embracing. Under the last heading of this paper a short résumé concerning hormones, their commercial names, and a few explanatory diagrams will be found.

The present article is an attempt to classify the confusion of ideas as far as possible. It is clearly understood that many statements may prove to be incorrect later. If dogmatic statements are made they are made only to emphasize our knowledge as it is at the present time. Such a paper must be superficial and it is written only to aid practitioners who do not have the opportunity of working in research with the aid of well equipped biological laboratories.

The subjects chosen to be discussed may be grouped under the headings—*inflammation, tumors, pathologic physiology, and endocrinology*. The necessity of giving credit where due in such a paper is not feasible and the author hopes that the lack of references to men responsible for outstanding pieces of work will be understood both by them and by their readers.

### NEW DIAGNOSTIC METHODS

First to be considered should be advances in the methods of diagnosis. It is now clearly established that certain urine and blood tests for the presence or absence of pituitary or



ovarian hormones are of great value Estrin<sup>1</sup> is present in the normal patient's urine and anterior pituitary prolan<sup>2</sup> is not In the blood of the normal patient estrin can be detected and occasionally anterior pituitary prolan In ovarian failure estrin should be absent and pituitary prolan present in both blood and urine, while in pituitary failure neither should be present in either Blood tests are difficult to do but the urine tests are perfectly satisfactory so that the findings in the twenty-four hour specimen of urine and the morning specimen of urine are sufficient Just before the menstrual flow the estrin content drops markedly and this fact should be taken into consideration when studies are made Following removal of the uterus, if both ovaries are retained, the findings are just as in normal women Removal of the uterus does not cause an early menopause if the ovaries are healthy and are left with an intact and satisfactory blood supply The table below showing urinary findings has been used with considerable satisfaction in our Ovarian Dysfunction Clinic Its absolute accuracy may be questioned, but as a working table its value is great

|                      | <i>Estrin</i> | <i>Pituitary<br/>prolan</i> |
|----------------------|---------------|-----------------------------|
| Normal               | +             | 0                           |
| Ovarian deficiency   | 0             | +                           |
| Pituitary deficiency | 0             | 0                           |
| Pregnancy            | +             | +                           |

After the test of a patient's urine has been reported, and more than one test should be made, the probable factor in the patient's difficulty should be manifest For instance a patient with no estrin and positive prolan would be considered to have an ovarian deficiency

Another valuable method of diagnosis is endometrial biopsy This can be carried out in the office either with or

<sup>1</sup>As used by the author the term estrin includes all chemical types of estrogenic hormones

<sup>2</sup>Anterior pituitary prolan is that substance from the anterior pituitary gland that brings about follicle formation, ovulation, and luteinization in the experimental animal ovary It is recovered from the pituitary itself Pregnancy urine prolan, or the so-called "anterior pituitary luteinizing hormone," is present in the urine of pregnant women and is that hormone that is responsible for the Aschheim-Zondek test and Friedman test It has been on the market for some time under the various commercial names described in the section on hormones

without a short anesthesia. The following methods are in vogue at the present time, the punch method, the suction curetté method, and the small cup curette method. By means of the punch and small curette a piece of tissue can be removed from a given place in the endometrium while the suction curette removes much more tissue but the area from which it was removed is not so definite. If, as has recently been reported, we are to find different types of epithelium in different areas of endometrium perhaps the suction method is best, as it removes more than one piece. The value of the biopsy lies in the fact that the pathologist should be able to tell whether or not a given patient has ovulated. The so-called "premenstrual, progestational, or secretory phase" does not occur without ovulation. Therefore if a specimen is removed about the twentieth to twenty fifth day after onset of a menstrual period secretion should be present, if it does not show secretion the patient may not be ovulating and therefore her flow comes from a proliferative or estrin phase and not from the corpus luteum or secretory phase. This fact might account for her menstrual abnormality or sterility. This simple test has been of immense value in determining late ovulation, early ovulation and anovulation and gives accurate evidence of the results of hormone treatment.

The measurement of the uterus is an important aid in investigation of the gynecologic patient. This is done with an instrument devised by Samuel Meaker and consists of an ordinary uterine probe marked in centimeters and a collar that can be moved up and down the shaft to allow readings of the length of the cervix from the external to the internal os and the length of the uterine canal from the external os to the top of the fundus. The normal measurements of the whole uterus to the cervix should be in the proportion of three to one, in the juvenile uterus it is as two to one, and in the infantile with its long conical cervix as one to three. These measurements are easy to obtain and may be the clue to the reasons for amenorrhea, dysmenorrhea, sterility, etc.

Congenital erosion of the cervix has been observed in both anatomical and function disturbances of the genital tract. The name is not a true descriptive term for the condition is not a true erosion but a maldevelopment of the cervix. The circular

strawberry-red area surrounding the external os of the virgin cervix is made up of endocervical glands and is a stigma of hypoplasia. The uterus is not normally developed if the endocervical glandular epithelium is not properly drawn up into the cervical canal. The "erosion" is the exposed endocervical epithelium. Unquestionably this type of cervix tells a story of underdevelopment and many instances have been seen in our clinic that prove the importance of the consideration of this lesion in proving hypoplasia. It is a stigma of lack of normal development and should be carefully watched for.

Molimina or premenstrual feelings, probably due to increasing estrin production, are of importance. The normal woman can usually tell when her next period is due by the "feelings" of depression, easy weeping, backache, bloating, bearing-down, painful breasts, pimples, cramps, and whitish discharge. Many other sensations are noticed but the above are the most common. If a patient with amenorrhea has such rhythmic feelings it is certainly a sign of ovarian function for with the ovaries removed these feelings vanish. With the ovaries present and the uterus out molimina are still present. Such "feelings" may give a clue to the proper time to start treatment in the amenorrheic patient and the dates of such occurrences are of considerable worth. A lack of molimina in the amenorrheic patient may indicate a primary ovarian dysfunction and in a patient such information would be of enormous value.

Hirsutism, or abnormal growth of hair, is a common finding in our clinic and is difficult to evaluate. Without doubt certain women have more masculine characteristics in their make-up than others, just as certain men have more femininity than others. Also certain races tend to moustaches and beards and hairy arms, while others do not. If the hirsutism has been present since youth its significance is not so great as when it suddenly appears. The recent onset of hirsutism in a woman may mean nothing serious or it may mean the onset of a masculinizing process due to pituitary disease (basophilism), adrenal cortex disease, or a masculinizing tumor of the ovary (arrhenoblastoma). Certainly such evidence is of importance.

In another field altogether are two investigative methods that are proving of more and more importance. Most of us

cannot interpret the findings correctly as yet but practice will prevent serious lesions from developing under our observation. Cancer of the cervix, next to cancer of the breast, is the most common lesion of malignant neoplastic nature that woman has. If earlier diagnosis is possible then we must all familiarize ourselves with the method. Schiller found that iodine in the form of Lugol's solution, if applied to the normal, healthy cervix, stained it a dark brown. He found that it stained scars, erosions of the cervix, and chronic inflammatory processes a lighter shade of brown but he also found that Lugol's solution did not stain leukoplakia or early cancer of the cervix at all. This lack of staining is due to lack of normal glycogen content of the cervical epithelium. Therefore, with a vaginal speculum and a nasal spray full of Lugol's solution, with the cervix gently wiped dry with cotton, a very important observation can be made by any one. If on such an examination a white patch of any size is discovered the patient should be investigated further. The piece of tissue should be examined microscopically to determine the type of lesion, and if leukoplakia the offending area or cervix should be removed, and if cancer the uterus should be removed or radium applied, depending upon the advice of the surgeon or gynecologist. Hinselmann has developed the colposcope (vagina scope) to a high degree of usefulness and his writings and the writings of others clearly describe the appearance of leukoplakia, premalignant or malignant conditions of the cervix. This instrument magnifies the cervical epithelium ten times and makes the observation of small areas of atypical epithelium easy. Without doubt small areas may be seen that cannot be detected with the naked eye and large areas of abnormal tissue may be studied more carefully. Mucous secretory ducts, Nabothian cysts, irregularities in the smooth epithelium, and leukoplakia are easy to detect. Not all can own such an instrument, but there is no doubt about its value and its usefulness.

#### INFLAMMATION

Advance has been made in the interpretation of vaginal discharges. The most important is the recognition of the *Trichomonas*. This flagellate is frequently found in women

without symptoms but more often it is the cause of an irritating, odorous, profuse, white to yellow discharge. The patients frequently complain of a disagreeable feeling and irritation of the vulva and inside of the legs. Recognition is easy. A drop of discharge is placed on a glass slide with a drop or two of warm water added and covered with a coverslip. The high dry power of the microscope is used. The light is cut well down and structures the size and shape of pus cells can easily be seen jerking their way in the moist smear. They may be confused with phagocytic cells, but if watched carefully small whips can be seen at the periphery of the cell. The complete configuration of the trichomonas is rarely seen. These organisms are most often part of a mixed infection so that pus and bacteria are commonly present.

The treatment is not easy. Many cases are encountered but few cured. The variety of the methods of treatment show that there is no specific one. It is very important to instruct the patient to wash the vulva and perineum carefully after each defecation, she must also be instructed to wipe the anus from front to back and not back to front. In the office the vagina should be gently cleaned out with dry cotton or cotton soaked in green soap and water. Then the treatment can be applied. The vagina may be painted with pure pyroligneous acid and soft tampons covered with Lassar's paste inserted to balloon out the vagina. The tampons are removed in forty-eight hours and douches of one teaspoonful of a 1:100 solution of oxymercure of mercury to one quart of water are used daily. Another treatment after cleaning of the vagina is to use picric acid vaginal suppositories 1 grain each night, washing out the suppository each morning with a douche of sodium perborate, one teaspoonful to one quart of warm water. The patient should be warned to wear her menstrual gear at night, as the picric acid stains the night clothes. Stovarsal powder in a powder blower used two to three times a week in the office frequently clears the condition. Recently Devegan tablets (Winthrop Co.) have proved effective. Two tablets are placed high in the vagina at night and are douched out in the morning with one teaspoonful of sodium perborate in one quart of warm water. The treatment continues till tablets and douches are no longer necessary.

All of the above treatments make the patient comfortable, but do not guarantee that the infection will not return if the treatment is neglected or given up. Cures sometimes seem easy but recurrences are easier. There is no one method of absolute cure.

Monilia infections are of a similar sort and cause a vaginitis with a more watery discharge occasionally with white pieces of tissue in it. The diagnosis is made by staining some discharge on a slide with Gram's stain and looking for yeasts and long branching mycelia. The treatment is cleanliness, careful wiping of the vagina and the use of alkaline solutions, such as mild sodium bicarbonate douches, and glycerin and borated sodium bicarbonate suppositories. The use of 1 per cent aqueous solution of gentian violet painted over the vagina is of considerable value.

Much has been written of the treatment of vulvovaginitis of gonorrheal origin in children. This infection is very persistent and resistant but the knowledge of the ability of estrin to change the infantile vaginal mucosa to adult squamous epithelium is the basis of a new treatment. Five hundred international units of estrin by mouth daily will suffice to change the epithelium. When the epithelium becomes adult in type the gonococcus is supposed to remain no longer as an inhabitant of the vagina. There is no doubt that this form of treatment will change the lining of the vagina. Although relief of symptoms is early and easy and the vaginal changes can be watched by vaginal smears under the microscope, nevertheless the cure of this condition by this method is not always accomplished. Certainly it is a step forward and no untoward reactions have been seen in the children. Occasionally, if the dose is too large, the patient will complain of swelling in the breasts, and in one case a moderate amount of vaginal bleeding ensued.

The treatment of pruritus vulvae is still difficult. Absolute cleanliness, the use of carbolic acid lotions and other mild analgesics are helpful, but if the pruritus is persistent and the discomfort of the patient extreme, alcohol injection under an anesthetic may be tried. If one to 2 drops of 95 per cent alcohol are injected  $\frac{1}{4}$  to  $\frac{1}{2}$  inch apart at the periphery of the area of pruritus relief can be obtained in some of these

very difficult cases The vulva may swell after the treatment and remain painful for a few days Not over 10-20 cc of this solution should be used at one time

It should not be forgotten that diabetics frequently have itching of the vulva and a urine analysis must always be done Many cases of pruritus are due to epidermophytosis and eradication of this infection is frequently followed by relief The use of mild salicylic acid and benzoic acid preparations, the strength depending upon the amount of cracking and fissuring of the skin, is advocated Cleanliness, and avoidance of scratching are important factors in the cure

The severe itching and discomfort of leukoplakic vulvitis and kraurosis vulvae are best handled by radical excision of the vulva Both lesions are precancerous and radical surgery cannot be criticized Section of nerves crossing the perineum is advocated but often falls far short of cure and if operation is to be done vulvectomy with removal of diseased tissue is probably safest

### TUMORS

Tumors of endocrine significance are not uncommon but recognition of them has only been recent Certain of these tumors are accompanied by subnormal development of the host, others cause masculinization and still others, femininization The knowledge of the existence of such tumors is important and if a patient with certain peculiar characteristics has an unusual tumor the cause and effect may be evident The ovariectomized or combination testicle and ovary is rare, and is often accompanied by hypospadias The testicular tubular adenoma of Pick is a type of arrhenoblastoma (arrhenos meaning male) and may cause mild masculinization and failure of the ovaries and removal allows femininity to redevelop The suprarenal hypernephroma either of the suprarenal gland itself or of the ovary causes a severe masculinization In cases of masculinization of recent development such lesions must be looked for In basophilic adenoma of the pituitary (Cushing's syndrome) amenorrhea and masculinization with marked hirsutism are not uncommon The dysgerminoma or seminoma of the ovary may be accompanied by a neutral development of the patient, the sex organs being rudimentary or with only partial develop-

ment Femininizing tumors are of the granulosal, lutein or thecal types and are accompanied by the secretion of estrin and by menorrhagia before the menopause and abnormal bleeding and resumption of periods after the menopause The granulosal cell tumor is more frequently malignant than benign Its removal with removal of its estrin secretion allows the patient to return to normal The luteoma, a rare tumor, is probably a granulosal cell tumor that has changed, as it physiologically could, into a tumor of luteinized granulosal cells The existence of luteoma is often questioned These various neoplasms must be borne in mind for neglect or ignorance of them might result in a disaster for their malignancy, excepting the first two, cannot be underestimated

#### OVULATION

Much work has been done in attempts to establish the time of ovulation If ovulation time were accurately known the treatment of sterility would be aided and the prevention of conception made easier The ovum is supposed to live but twenty four hours and the spermatozoön for three days, therefore if the time of ovulation were accurately established this time could be avoided for four days as a method of contraception or be used to aid in conception The consensus of opinion seems to be that ovulation takes place from the twelfth to the seventeenth day after the onset of the menstrual period Therefore from the ninth to eighteenth days after the onset of the catamenia is either the time to avoid or to indulge in intercourse, depending upon the result desired Some patients can easily determine the exact time of their ovulation for they notice a sensation of gas or discomfort in the abdomen at the midmenstrual point. This happening is probably due to ovulation and if the pain or symptoms are exaggerated the patient is frequently operated upon for appendicitis and a normal appendix removed Careful inspection of the ovaries at the operation would disclose the fact that a follicle had just ruptured and coagulum and blood would be found in the pelvis Certain other patients notice a regularly occurring mid menstrual flow or pink discharge which is due to bleeding probably by diapedesis from an endometrium congested at the time of ovulation Because of the drop in estrin that



occurs at this time bleeding occurs Careful questioning of the patient regarding every possible factor in the menstrual cycle often proves of great value

Operations in young girls for chronic appendicitis are often due to ignorance of the physiology of the ovary Lack of a proper exploration of the patient's pelvis fails to reveal the true reason for the pain Girls with mild pain at the intermenstrual point can be carefully watched and if no untoward symptoms develop surgery can be avoided This at least is an important outcome of our more enlightened knowledge of normal ovarian physiology

### SEX DETERMINATION

Although many have searched for a means of determining the sex of the unborn child no discovery of importance has as yet been verified Certain suggestive findings have been reported but none that has proved satisfactory Studies of the blood and urine to determine the presence or absence of estrin to prove the sex in cases of hermaphroditism and patients without vaginas have no value It is not possible to establish the proper sex by hormone determination

### FRIGIDITY

To relieve frigidity in the female has frequently been the goal of medical men and gynecologists The problem has not been satisfactorily answered as yet but certain investigators while giving patients huge (100,000 to 200,000 I U ) doses of estrin to bring about menstruation in the amenorrheic have noted increase in libido during treatment This opens a field for speculation and the use of estrin may prove of value in some cases It is just as sure, however, that in other cases it will be of no value whatsoever Smaller doses may be tried for the expense of huge doses of this hormone is too great for most to bear The reaction of patients after the menopause is of interest—some patients are completely frigid, some have a greater libido, and some are unchanged Perhaps it is lack of estrin that determines the problem, but there is no definite proof as yet, although estrin has aided frigidity in certain cases Some patients after x-ray treatment given to destroy the ovaries, note an increase in libido for a short time and after

a few months a great loss of feeling. Unquestionably all patients who are to have x ray treatment over the pelvis should be warned of the possibility.

Careful and thoughtful psychological examination is the most useful method of investigation and sympathetic history taking may unravel an unexpected situation. Certainly dyspareunia or painful coitus makes for frigidity and if this can be cleared up frigidity may vanish.

### STERILITY

The study of sterility and fertility is fascinating and the number of investigators enormous. There are certain facts that seem important and are rather new. The anovulatory cycle is of paramount importance—though suspected as a possibility for years, only lately has the fact been established. Many women flow irregularly and a few absolutely regularly without having a graafian follicle rupture. Of course if ovulation does not occur no woman can conceive. To establish the presence of ovulation it is necessary to curette the endometrium or do an endometrial biopsy. This should be done on about the twenty fifth day after the onset of menstruation. If such a piece of tissue shows only a proliferative or estrin phase and no premenstrual or secretory phase and the patient flows shortly afterward she can be considered as going through an anovulatory cycle. There is no absolute cure for such a condition and before any treatment is instituted the test should be repeated, for it has frequently been noted that after such a curettage or biopsy the patient has become pregnant. It has also been noted that after an endometrial biopsy the next biopsy shows a premenstrual or secretory phase. These facts probably explain the frequent occurrence of pregnancy following dilatation and curettage, following the Rubin test, and following lipiodol injection of the uterus to determine the patency of the tubes. Trauma of the cervix or the uterus may be the responsible factor (just as in the rabbit, ovulation does not occur without copulation). Trauma followed by ovulation, no period and conception—this sequence of events has occurred so frequently that the probability is perhaps a fact. Another method of inducing ovulation is to use one of the anterior pituitary sex hormones (not

pregnancy urine prolan, the anterior pituitary-like hormone) in an endeavor to stimulate follicle formation. It is not certain that it always occurs and that if it does that ovulation takes place, but it should be a more satisfactory method of treatment than the use of prolan from the urine of pregnant women. The use of pregnancy urine prolan in sterility work is fraught with danger, for many investigators feel that this substance causes changes in the ovary suggestive of atresia, the opposite effect to the desired one. Estrin, as it does nothing to the ovary and as it is supposed to inhibit the action of the pituitary, should not be used. Yet certain men interested in sterility work have no hesitancy in reporting its success occasionally, but the explanation is not known.

Certainly in sterility cases the measurement of the uterus is important. Many a uterus that feels large on examination is really infantile or juvenile in structure and although a patient with this type of uterus may become pregnant, nevertheless in a sterility case knowledge of the hypoplasia is of great importance.

Thyroid is an important agent in treating sterility patients and many have conceived after taking small amounts ( $\frac{1}{2}$  grain daily) for short periods of time. In patients with low metabolisms this is of great importance, but even in those patients with normal metabolisms treatment with thyroid has proved of value.

A factor frequently overlooked but of great significance is the condition of the ovum or spermatozoon. The so-called "blighted" ovum is due to a defective ovum or sperm and it is very possible that defective germs are produced because of an intrinsic fault in a patient's gonads. The production of such a defective ovum may allow menstruation in all its phases to take place but completed pregnancy may never occur.

Habitual abortion is not actually a problem of sterility, yet the patient who aborts is sterile as far as a living child is concerned. The problem here is perhaps overactivity of the estrin-primed uterus due to lack of the quieting corpus luteum hormone, progesterin. The first endeavor to treat this condition was the attempt to create an effective corpus luteum in the ovary by using pregnancy urine prolan to stimulate luteinization. Now that we suspect that this hormone (preg-

nancy urine prolan) does not cause luteinization it is not wise to use it. Progestin is now on the market under the trade names of Corlutin and Proluton. This substance, if potent, should be able to quiet the estrin irritated uterus and in some cases it has done so, preventing habitual abortion and allowing pregnancy to proceed to its conclusion. The dosage should be  $\frac{1}{10}$  to 1 rabbit unit two to three times per week.

Apparently vitamin E is important in patients who abort habitually. It has been shown that lack of vitamin E causes death in utero. This vitamin is easily available in lettuce and in wheat germ oil. The latter is now on the market and 5 to 10 drops daily is a sufficient dose.

### THE BREAST

The breast is acted upon by estrin and progestin. Estrin acts upon the duct system and progestin upon the alveoli. After the breast has been properly primed by these two hormones during pregnancy prolactin (from the anterior pituitary) acts upon it and causes lactation. Lactation has not been produced in castrated women by this method but marked and suggestive changes have occurred in the breast.

The premenstrual painful breast may be due to over stimulation by estrin. To relieve the pain and discomfort it is necessary to diminish such secretion. One method would be x ray treatment of the ovaries or destruction of the pituitary secretion that stimulates the ovaries. Obviously these are not the proper methods, therefore, inasmuch as we believe excess of estrin will inhibit the pituitary gland estrin should be used before the oncoming period and omitted about five days before it is due. Thus the pituitary would cease secreting and in the remaining five days before the oncoming period would not have time enough to produce more estrin from the ovary. Therefore the estrin content would be reduced and consequently less pain occur in the breast. This theory is not without its defects but surprisingly enough the treatment is effective in many cases. Six hundred international units of estrin given daily except for the five days before the oncoming period has proved effective.

Another condition in which to use our knowledge of breast physiology is in the breast that lactates after cessation of

nursing or the breast that lactates and swells at the time of weaning Prolactin (an anterior pituitary hormone) will not act in the presence of estrin, therefore large doses of estrin should stop lactation It has been found that if live pieces of chorion are left in the uterus after delivery lactation is prevented This is because the chorionic tissue secretes estrin, which prevents the action of prolactin

It is conceivable that chronic cystic mastitis, a disease more frequent in the unmarried woman with unused breasts, may be due to constant stimulation of the duct epithelium by estrin with no letup of this stimulation such as occurs in pregnancy and lactation

Treatment of the bleeding nipple by means of estrin has been advocated by Mazer, who believes that excessive anterior pituitary lobe hormone causes an abnormal response of the alveolar system He believes that this type of mazoplasia may be accompanied by papillary growth in the upper ducts and is due to lack of estrin as well as increase of anterior pituitary hormone The treatment should be inhibition of the pituitary by more estrin and he has found that this treatment is satisfactory to check pain and stop bleeding That there is danger in such a method of treatment is unquestionable, for bleeding from the nipple may be due to a papilloma and this papilloma may be a serious one and not a benign one Also certain cancers of the breast are accompanied by bleeding and differentiation between the two is difficult

One of the most satisfactory forms of treatment of breast discomfort is the use of a proper supporting, as contrasted to pressure, brassiere This simple expedient is frequently overlooked and its importance cannot be overestimated

#### PREGNANCY TESTS

The Aschheim-Zondek and Friedman tests are from 90-98 per cent perfect Most of the failures have a real explanation and some negative results are proven positive upon a repeat test It is not wise to conclude that a patient is not pregnant if signs point toward pregnancy till at least two tests have been completed False positives are often due to different types of female sex dysfunctions

The use of pregnancy tests to diagnose extra-uterine preg-

nancy has not met with universal agreement. The Friedman or rabbit test should be used because of its quickness. If an extra uterine pregnancy is suspected and the patient is in excellent condition and not bleeding, the test should be done, but if the patient is ill and there is an abdominal emergency, operation is the proper treatment and an attempt at too fine a diagnosis might prove disastrous. The test should be positive as long as any living chorion is present in the tube or abdomen.

The Aschheim Zondek or Friedman test should be negative seven days after termination of pregnancy. The presence of living chorionic tissue will continue to give a positive reaction. If such a reaction persists the question of retained products or of chorionepithelioma should be raised. High titers of ten to fifty times the usual amount of prolan should be considered as a serious finding. In hydatid mole the test is high and in chorionepithelioma very high. If after a mole, chorionepithelioma, or pregnancy, a test that has been negative becomes positive a very serious condition has probably arisen, either tumor has developed or recurred or a metastasis taken place. If the test persists after miscarriage, pregnancy, or mole a curettage should be done and if it is positive after this a diagnosis of possible tumor must be made and hysterectomy is justified. If the test persists after the hysterectomy then it is probable that a metastasis has taken place.

Certain teratomas of the ovary containing chorionepithelioma give positive tests, and the finding of a tumor in the pelvis not a pregnancy with a positive test should make one suspicious of this type of lesion.

#### AMENORRHEA AND DELAYED MENSTRUATION

Amenorrhea is an expression of absent ovarian function. If primary, its cause lies in the ovary itself, and if secondary, in some outside influence that affects the ovary. In the treatment of such a condition it is necessary to know the type of amenorrhea the patient suffers. A study of the hormones present in the urine helps. If estrin is absent from the urine and prolan is present, the ovary is primarily at fault. If, however, prolan (from the pituitary) is also absent the ovary may be able to function but stimulation of it is absent. Endometrial biopsy will also indicate whether the ovary is

going through any sort of cycle or whether it has ceased to function. There is no doubt but that influences other than the pituitary may be at work. For instance, in hyperthyroid states or myxedema, the ovary often ceases to function. Any debilitating disease such as tuberculosis, allows the functions least necessary to life to cease. As the reproductive function is the least necessary for carrying on life, it is early affected in disease. Once the reason for the amenorrhea is established intelligent treatment can be carried out. If the cause is prolonged illness it can be treated with hope of cure. If pituitary dysfunction is responsible, then the hormone of the anterior pituitary should be tried. Doses of Prephysin (Chappel) from 25 to 200 units should stimulate the follicles of the perfectly good ovary and ovulation may follow. The use of this extract has certain dangers as overstimulation of all follicles might result. It is conceivable that too many of the follicles might be stimulated and this might have serious consequences. If the ovary itself is at fault the stimulation with pituitary hormone is again advised though the result may be unsuccessful, for if the ovary is too far atrophied then no stimulation will revive it. Such treatment is, however, perfectly justifiable.

Estrin and progestin can be used to bring about a menstrual period but as ovulation does not occur in such instances its value can only be psychic and the expense of the large doses necessary (100,000 to 200,000 international units of estrin and 10 to 50 rabbit units of progestin) are prohibitive. It is possible that such a treatment by bringing about a menstrual cycle might cause it to continue, but there is no reason for expecting such a result.

It has frequently been noted that patients with thyroid underfunctions are amenorrheic and the wise use of this extract has proved of value in many instances. Thyroid is of real value in amenorrhea and should always be tried, but the basal metabolism should be used in conjunction with it.

Estrin itself may cause the endometrium to develop and proliferate and when withdrawn may allow bleeding to occur. This bleeding is bleeding from the proliferative type of endometrium only as no secretory change can be brought about by estrin alone. Ovulation has not occurred. Psychologically

this bleeding may be of value to the patient but it is not a physiologically perfect result.

The amenorrhea of obesity and certain functional disturbances as well as those due to wasting disease are the ones most likely to respond to treatment. Real deficiencies such as pituitary or ovarian are much less likely to respond.

There are types of temporary amenorrhea associated with follicular cysts of the ovary that can be treated either by means of surgery (excision or puncture of the cyst) or even rupture of the cyst by bimanual examination, though this latter type of treatment is not recommended.

The use of estrin to develop a small uterus, especially when the uterus is considered the organ at fault, has its advocates and if large doses (1000 to 3000 I U of estrin) are used daily over monthly intervals, it is conceivable that such an effect could be brought about.

Amenorrhea should not be allowed to continue untreated in girls of child bearing age, because if the delay in the catamenia is allowed to progress beyond a year, cure of the condition is very unlikely. Prompt treatment of the undernourished, sick, and underdeveloped, and the use of thyroid and pituitary hormones should be instituted early in the dysfunction if results are to be obtained. The same treatment should be accorded those individuals who have a delayed onset of periods (menarche) and great industry should be employed to bring about the onset of flow. If a girl has not had a period at the age of sixteen then treatment should be undertaken. Proper hygiene, endometrial biopsy, anterior pituitary prolan, thyroid, etc., should be employed early.

Certain anemias of youth are often accompanied by amenorrhea and such blood dyscrasias should be investigated and the anemia corrected. A secondary anemia of the chlorotic type may be responsible and the response of the dysfunction following treatment of the anemia with iron is often striking.

Cysts of the corpus luteum with a persistent secretory phase and decidual formation in the endometrium are possible and although cases have been reported in the literature they are not common. Such pathology should, however, be searched for and if found, the cyst should be excised.



## DYSMENORRHEA

The study of dysmenorrhea is far from finished and the problem is so great that only the barest outline of procedure and treatment can be outlined. Dysmenorrhea occasionally responds to psychotherapy, to medical treatment, to hormone therapy, and to surgery. Many are the tools of the profession in the treatment of the condition but few the complete cures.

Pelvic examination in patients with dysmenorrhea may disclose a small, underdeveloped, anteflexed or retroflexed uterus, or a small-sized uterus in normal position or retroversion, or a large boggy uterus in retroversion, or even a normal-sized uterus in good position. Pelvic inflammations, intramural or submucous fibroids may also be possible causes and must be borne in mind.

The typical uterus of the patient with dysmenorrhea is either ante or retroflexed and is usually of smaller rather than larger development. Measurement of the uterus if the hymen is ruptured, may give a clue to the proper treatment, for if it is underdeveloped attempts at further development should be carried out.

That psychic disturbances are causal factors cannot be denied but often after careful investigation with mental relief to the patient dysmenorrhea continues. Without doubt dysmenorrhea may be made much worse by an over-solicitous mother and over anxiety at the time of the catamenia is an undoubted factor. However, such patients may have dysmenorrhea after marriage when away from maternal solicitude and not be relieved till after the birth of a child. There is a goodly percentage of cases in which dysmenorrhea recurs after childbirth, to the consternation of the doctor, who said that childbirth would cure it. There is no absolute cure except hysterectomy and this should not be considered until the very last resort.

The first treatment should be carried out by the family doctor, who should try to correct any worries that the patient may have and he should warn the anxious parent against pitying the child too much. The health of the patient should be noted and any sign of underdevelopment or undernourishment corrected as far as possible. If the uterus, on rectal

examination, is found to be flexed forward or back and of small size, then the use of estrin is indicated. Whether or not growth actually occurs is not altogether settled but it is theoretically sound and worth trying.

The inhibiting action of estrin is another reason for its use and certain cases are much relieved by giving subcutaneously 50,000 I U seven days before the onset of the coming period in one dose. Estrin, when used in this fashion, is supposed to inhibit the pituitary gland from secreting prolactin A that in turn causes secretion of estrin in the ovary. If we believe that estrin sensitizes the uterine musculature, which it probably does, then we can lower the amount of estrin present at the time of menstruation by the above method. By giving a large dose before the oncoming flow we prevent the pituitary from causing the ovary to secrete more estrin and in the seven days left before the period is due there will not be time to manufacture more and the estrin given subcutaneously will have been used up. Thus at the time of onset of the catamenia the estrin content should be low and the uterus not as sensitive. This method has been successful many times and its use is advocated. The reasoning for its use may not be correct but the results obtained justify the therapy.

It is known that the hormone of the corpus luteum, progesterin, causes a cessation of motion in the uterine musculature brought about by estrin. It would seem logical, therefore, to use progesterin to quiet the sensitized uterine musculature and thus cause a cessation of cramps. This should be a valuable method of treatment now that progesterin is available for use. The dosage should be as large as the individual patient can afford and from 1 to 50 rabbit units could not be too great a dose.

The above method has been tried before but in a different way. Pregnancy urine prolactin was supposed to cause luteinization and thus bring about a secretion of progesterin *but* until it is more definitely settled that pregnancy urine prolactin does affect the ovary and how it does its use is theoretical only. The consensus of opinion now seems to be that pregnancy urine prolactin produces atresia in the ovary and that although theca luteinization may occur real luteinization does not. That these observations are correct is another question and only

further study will prove them. Certainly the effects of pregnancy urine prolan on the ovaries of mice and the presence of lutein cysts of the ovary in hydatid mole and chorionepithelioma (when the urine contains immense quantities of pregnancy urine prolan) makes it difficult to doubt the luteinizing power of pregnancy urine prolan.

When the above methods of treatment have been tried and have failed the use of dilation in the office with small dilators is advised. It has been noted that after a uterus has been measured with Meaker's hysterometer in a patient with dysmenorrhea that the next period may be less painful, and recently it has been suggested that small-sized uterine dilators be passed through the internal os as an office treatment for the same reason. This method of treatment, if done with surgical asepsis, should prove of great value. Dilation, as carried on this way, may be too little and the patient should then be subjected to proper dilation under an anesthetic. This stretching should be thorough and carried out for at least fifteen minutes. At the same time, while the patient is under an anesthetic, it should be noted if there is a tight band about the internal os. This band, similar to the hard band-like tissue found about a pyloric stenosis in infants, can be easily felt on rectal examination. It is not difficult by placing a knife in the cervical canal as far up the internal os and with a finger in the rectum to make an incision directly posterior and cut across the hard band. A small piece of gauze is then placed in the incision to keep the constricting band open and from healing in its original position.

If all treatment has failed so far the patient should have an abdominal operation and a suspension of a flexed or retroverted uterus. At this time a resection of the presacral nerve or superior hypogastric ganglion should be carried out, for this method of treatment has given the highest percentage of complete cures of any procedure except hysterectomy. There are failures even from this operation and the failures are probably due to anomalies of these nerves and lack of section of them. This cannot be avoided and although results are good in nearly all cases they are not absolutely perfect.

The last treatment of all for dysmenorrhea should be

hysterectomy and to advocate this is to fail in the treatment of a condition that in most instances can be helped if not completely relieved

### FUNCTIONAL BLEEDING

Most bleeding of the functional type is due to an ovarian dysfunction and whether the real cause is primary ovarian or primary pituitary is not essential to the understanding of the now known physiology and pathology, and consequently the treatment.

Bleeding accompanied by hyperplasia of the endometrium is the most usual type. In this type of bleeding the uterus or end-organ of the genital tract may be small or large, may contain fibroids or may not. The endometrium in most instances is thick, occasionally polypoid but occasionally very thin. In many instances, microscopically, it shows typical hyperplasia. The hyperplasia is due to either too much estrin or to continuous estrin acting upon it. No progestin influence is present. The ovaries contain a follicular cyst or cysts which are cysts of pathologic physiology and are not neoplastic. These small cysts contain estrin in a greater or lesser amount. There is no evidence of any corpus luteum formation. The pathology of the pituitary in these cases is not known at the present time. The urine of such a patient contains very little or no estrin during the bleeding but after the bleeding has ceased estrin reappears in the urine. The physiology is about as follows: the pituitary being abnormal, produces prolactin A continuously, this in turn causes the persistence of a graafian follicle and due perhaps to lack of prolactin B, ovulation does not take place. The follicle continues to develop, becomes cystic, and fills with fluid containing estrin. This persistent estrin production causes the endometrium to develop beyond the normal estrin phase and the hyperplasia succeeds the normal proliferative endometrium. As the estrin persists it inhibits the production of prolactin A by the pituitary. Then lack of pituitary prolactin A in its turn causes a drop in the production of estrin and as estrin diminishes in strength in the cyst sloughing of the endometrium occurs and bleeding takes place. (It is well known that estrin withdrawal is followed by bleeding.) The physiology and

pathology of this type of bleeding is known as metropathia hemorrhagica or Shaw, Type I bleeding. The treatment of the condition is obvious. If the cyst could be ruptured the sequence of events would be interrupted, if a luteinizing hormone could be used luteinization of such follicles would follow and the endometrium would change from the proliferative hyperplastic phase to the secretory or corpus luteum phase. Or if a potent corpus luteum hormone could be given in large doses it should change the endometrium to the secretory phase and the later withdrawal of progestin would be followed by menstruation from a secretory phase. (It is now known that if both estrin and progestin are used withdrawal of estrin in the presence of progestin does not allow bleeding but withdrawal of progestin does allow it and it is menstrual [secretory] in type.)

Any method that brought about ovulation in such bleeding cases would be followed by luteinization and thus the normal cycle would be reestablished. It is known that endometrial biopsy and curettage may stimulate ovulation just as copulation with a buck rabbit is necessary for the female rabbit to ovulate. Biopsy and curettage by traumatizing the cervix may be the causal factor in ovulation in these cases and thus be responsible for the return of such cases to a normal rhythm.

The treatment of this condition by means of hormones is not as perfect as it should be theoretically. Estrin by inhibiting the pituitary should stop prolactin A from causing estrin secretion and thus should allow normal events to follow, but such does not seem to be the case. The use of anterior pituitary prolactin, containing as it does some luteinizing factor, should permit luteinization to take place and thus bring about proper changes in the endometrium. It is said to accomplish this in some instances.

Pregnancy urine prolactin, known as the anterior pituitary luteinizing hormone, was considered to bring about luteinization and therefore proper changes in the endometrium, but this is all denied now, as it has been shown that this hormone only causes atresia of the ovary and not luteinization. It does, however, cause theca luteinization and it is possible that this type of luteinization may have some effect on the endo-

metrium Following the endometrium by means of endometrial biopsy after the use of pregnancy urine prolan is the way to test the efficiency of the method and although in many instances the endometrium does not change, in others a secretory phase has been recognized It is felt by some that this hormone causes the maturation of a follicle, ovulation, and a corpus luteum formation and thus the absence of many active follicles and corpora lutea in the ovary after treatment is explained In other words, a single follicle matures as it should and a normal rhythm is brought about The suggestion of a bleeding factor being responsible is difficult to accept It is certainly true that in many instances the use of pregnancy urine prolan advocated by the commercial houses and in the doses recommended by them does cause cessation of bleeding and a return to normal Its use is advised but the exact nature of the physiology is not known

The use of real anterior pituitary prolan seems more sensible, it may cause the development of follicles and when ovulation follows the cycle returns to normal Enough clinical experience has not been had to state that this is the best method of treatment but it certainly should be considered and its use is definitely justifiable Overtreatment might be dangerous because of overstimulation of follicles

It is conceivable that the use of both pituitary prolan and pregnancy urine prolan in sequence might be of value The first to cause follicle formation and the second to aid in continuing the follicle on to proper luteinization

Deliberate rupture of such a persistent follicle would be sound treatment, for interruption of this "middle man" would take pressure off both the pituitary and the end organ, the endometrium Such treatment would be heroic and although it has been accomplished without disaster to the patient with a cessation of bleeding, it is certainly not advocated

There are other types of bleeding of functional type and these will be mentioned briefly At the time of ovulation at the midmenstrual point there is a great congestion of the endometrium and when the estrin level drops, as it does at ovulation, the spilling over of a small amount of blood is often noted This is a normal process and needs no treatment.

The type of bleeding with a bimonthly rhythm is due to

too frequent ovulation and the exact reason for it is not clear. Too many corpora lutea are found in the ovaries of such patients and though the cycles are too frequent they are nearly normal in character. Inhibition of the pituitary by the use of estrin might help such a condition, and the use of pregnancy urine prolan has been proved of value.

### THE MENOPAUSE

The treatment of the menopause is one of the triumphs of female sex hormonology. At the menopause, whether artificial or natural, certain definite findings are present in the urine and blood. There is a fall in estrin to zero and an increase in the anterior pituitary hormone, prolan A. Hot flashes and nervous phenomena follow ovarian exclusion and they may be extremely severe or mild. Large numbers of hot flashes cause sleepless nights and great embarrassment in the presence of friends. To aid such conditions many advocate the use of bromides and luminal and to a certain extent they are successful. The use of estrin, however, either subcutaneously or by mouth, is miraculous and the well-being of the patient as well as a great reduction in the number of flashes occurs almost as soon as treatment is started. The treatment must be kept up, however, for an indefinite period of time, as it is not accumulative. Slowly the patient finds the correct dose that makes her comfortable and her relief is great. When treating the menopause with estrin the appearance of estrin in the urine is not the most important finding in the successful cases. Drop in the level of prolان in the urine is greater evidence of successful treatment.

The dosage should be from 200 I U daily to 6000 I U daily, by mouth, and from 1000 I U to 50,000 I U subcutaneously one to three times per week. The dosage must be worked out for the individual patient but with persistence nearly all women suffering from the menopause can be nearly completely relieved.

### THE HORMONES

The sex hormone of the anterior pituitary gland (prolan) may be purchased as gyantrin and prephysin. The ovarian hormone estrin is for sale under various names—theelin,

theelol, emmenin, amniotin, progynon, progynon B, folliculin, menformon and sistomensin. The ovarian hormone progesterin can be purchased under the name of corlutin and proluton. Pregnancy urine prolant (not to be confused with the anterior pituitary hormone prolant) can be purchased as antophysin, antuitrin S, follutein and A P L. With this ammunition we should be able to approach any physiologic upset in the female genital tract. Unfortunately all the commercial hormones

—PROLAN—

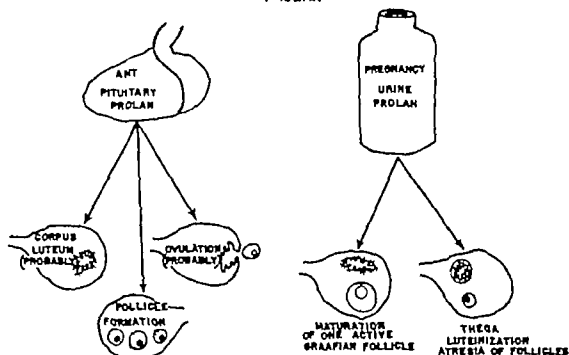


Fig 170—The two types of prolant. The anterior pituitary prolant is a stimulator of follicle formation, it causes ovulation and later corpus luteum formation occurs. Pregnancy urine prolant is in dispute. It probably causes the maturation of a fairly well-developed follicle and causes ovulation and luteinization. On the other hand many say that it only causes atresia of follicles and theca luteinization and fails to develop any activity in the ovary at all. These questions must be settled by further investigation.

do not work on humans as they do in the laboratory. There are however certain effects that are of great importance and we can reason our form of treatment from this knowledge. The anterior pituitary sex hormone prolant containing as it does a moderate amount of the luteinizing factor should be able to cause follicle growth and it is reported as doing so in the human. It may only carry the follicle on to full development and not through to ovulation but sometimes this occurs also. If this is true the cases of pituitary failure can be sub-



stituted for and the ovary made to go through its proper cycle, thus cases of pituitary amenorrhea should be helped and successful results have been reported. In cases of menorrhagia where a follicle cyst has been persistent it should be possible to create new follicles one of which might go on to proper ovulation thus relieving certain cases of abnormal bleeding.

Estrin is reported as developing the uterus, as causing hyperplasia of the endometrium, as developing the breast, as changing the vaginal epithelium of children to adult type, and

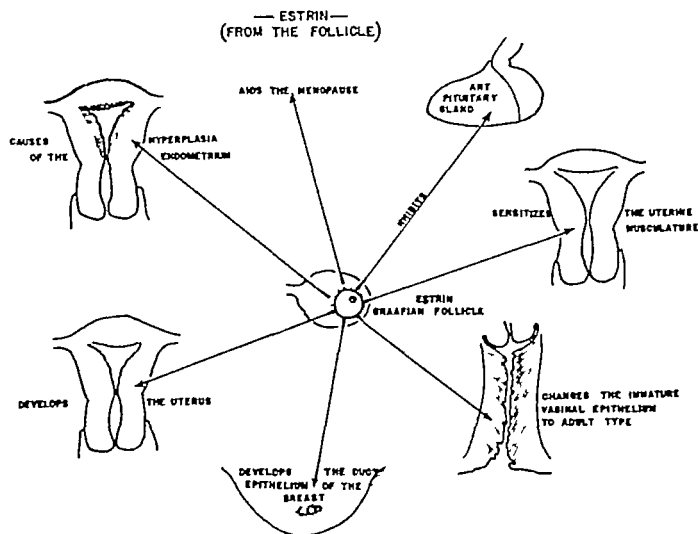


Fig 171—Estrin, and by this is meant any of the chemical forms of estrogenic hormones, has various activities. These are diagrammatically illustrated. It is possible that some of these will be proved untrue but for the present the above diagram gives a working scheme.

as stopping hot flashes. Estrin by its inhibiting effect on the anterior pituitary sex hormone should shut this hormone off and prevent the formation of more estrin in the patient's ovary. If this is possible then by judicious use of it and omitting it at the proper time a shortage of estrin can be brought about before the menstrual period. As estrin causes growth of breast epithelium, as it causes premenstrual feelings or molumina, and as it sensitizes the uterine smooth muscle to the oxytocic principle of the posterior pituitary, if it can be relied upon to check pituitary secretion, it should be

able to relieve painful breasts, lactating breasts, molimina, and dysmenorrhea. The methods of using it are described elsewhere in this paper.

Progesterin is an unknown quantity at present but if it acts as a neutralizer to estrin and if estrin causes the irritability of the uterine musculature it should be of value in dysmenorrhea (to prevent cramps), in habitual abortion by preventing irritation of the uterine musculature and should aid proper decidualization and nidation. There is some reason to believe it is of help in these conditions. If metropathia hemorrhagica

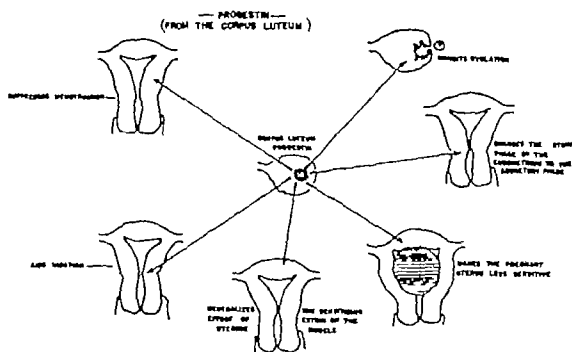


Fig. 172—The action of progesterin from the corpus luteum is diagrammatically illustrated. With this hormone available for use in clinics and practice many of the above actions can be proved or disproved.

is due to continuous estrin production with proliferative endometrium perhaps the use of progesterin to change the endometrium to the secretory phase might change the whole picture of this endocrine entity. It is considered the hormone that suppresses menstruation and that withdrawal of it is necessary for menstruation to commence.

The so-called "anterior" pituitary luteinizing hormone or pregnancy urine prolan is now an unknown factor. It was considered that it caused luteinization in the follicles of the ovary and hence changed the endometrium from the estrin phase to the secretory phase but both of these virtues are

denied it. It is now looked upon as acting upon the ovary in a dampening way, causing atresia of the follicles and thus not allowing proper development. It apparently does cause theca luteinization but as normal luteinization is supposed to be due to changes in the granulosa cells and not in theca cells it is difficult to understand its value, perhaps theca luteinization may be as important as granulosa luteinization but this is not known as yet. Pregnancy urine prolactin does help abnormal uterine bleeding, it checks the bleeding and occasionally changes are found in the endometrium accompanying the cessation of flow. Sometimes one looks for secretory phases in vain, but as the bleeding is checked by it, all sorts of bleeding factors are hypothesized. This hormone has a definite use in uterine bleeding of the functional type.

Thus as far as the therapeutics of female endocrinology is concerned we are not paupers and in the future there is no doubt but that more knowledge will be added and many of the functional disorders will be classified and properly treated.

## CLINIC OF DR ABRAHAM COLMES

BOSTON

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### RECENT ADVANCES IN THE TREATMENT OF HAY FEVER AND ASTHMA

#### INTRODUCTION

HAY FEVER and asthma can be considered jointly under one heading, because fundamentally they represent disturbances of a similar nature, one in the nose, the other in the bronchi.

When these two conditions coexist they may be due to the same provocative cause, as noted for instance, in pollen-sensitive patients in whom hay fever and asthma are often provoked by the same pollen, or on the other hand, they may be due to diverse exciting causes. Thus, a patient may have hay fever due to ragweed and asthma due to the ingestion of eggs. Such specificity in the exciting cause of the reaction and such selectivity in the site of reaction, are characteristic of the phenomena of human hypersensitiveness, and it is this hypersensitiveness which in the past has paraded under such diverse nomenclatures as "diathesis," "disposition," "idiosyncrasy," etc., and which has more recently been popularized under its newest adaptation, the term "allergy," that constitutes the fundamental disturbance of which asthma and hay fever are but clinical expressions.

Were we able to correct the fundamental disturbance which permits of the establishment of the hypersensitive state in man and its dependent clinical manifestations, the subject of treatment would be easily dismissed in but few lines. But since this fundamental disturbance is an inherited and integral part of the cellular structure of the body and since all chemical, metabolic and endocrine studies have so far failed to reveal its nature, we must accept it as a fixed and unalterable con-

dition and concentrate on those measures which tend to influence the hypersensitive state clinically. This can be accomplished to a greater or lesser extent in the following ways by relieving symptoms, by disposing of exciting factors, and by modifying the reactivity of the patient's tissues. Whatever advances have been made in the treatment of hay fever and asthma are directly related to the intelligent application of these measures. This in turn rests upon a clear understanding of the nature and mechanism of hay fever and asthma, and above all upon a correct diagnosis. Hence it is necessary, in the course of our discussion, to dwell upon these phases, even at the risk of digression.

### DIAGNOSIS\*

If the patient happens to be seen in the attack, the diagnosis of hay fever or asthma is self-evident. The characteristic spasmodic sneezing of the former and the audible spasmodic wheezing of the latter, readily suggest the nature of the ailment. Certain differential possibilities, however, must be borne in mind. Hay fever may be simulated by the common cold, by a foreign body in the nose and by polypoid degeneration of the nasal mucosa, in all of which, sneezing, nasal stuffiness and rhinorrhea may be present. These conditions, however, lack the itchy nose, palate, and eyes, which are so characteristic of vasomotor rhinitis and the strict seasonal incidence of symptoms when pollens are the causative agents.

Asthma must be differentiated from a number of other conditions which are accompanied by continuous or intermittent attacks of dyspnea. The nocturnal dyspnea of the failing heart is characterized by a history of progressive shortness of breath, by evidence of congestion in one or both bases and by the patient's favorable response to digitalis and morphine. The asthmatic breathing which often accompanies acute coronary thrombosis comes in the wake of an acute anginal pain, a symptom foreign to the asthmatic state. The stertorous and labored breathing, caused by a foreign body in the bronchi is differentiated from true asthma by its sudden onset and occurrence in a previously well patient, usually a

\* The term "hay fever" is used interchangeably with vasomotor rhinitis, for the former is merely a special variety of the latter.

child The dyspnea that may accompany an enlarged thymus, an aortic aneurism, a pleuritic or pericardial effusion or pressure upon bronchi from mediastinal tumors, is different from the spasmodic breathing of true asthma, with its prolonged expiratory phase, the scattered rhonchi in the chest, the elevated shoulders, fulness in the neck and dependent position which the patient assumes to facilitate respiration And yet bronchial asthma may coexist with myocardial disease, coronary sclerosis and all other conditions enumerated above In such instances treatment must be directed toward the amelioration of the coexisting conditions as well, lest our attempt to treat the asthma may fail

When seen between the attacks, in a symptom free period, the situation is somewhat different. Here the history of the case is vital The following points, when elicited, will enhance the possibility of a correct diagnosis

1 The spasmodic nature of the attack with freedom of symptoms in the interim, especially so in the early cases In the chronic type, symptoms in a milder form may persist throughout.

2 A tendency to periodicity, the attacks occurring sometimes either spring or fall, or sometimes on week-ends, or during the catamenia in the female, or only during the early morning hours

3 An incidence in the patient of other manifestations of allergy, such as, eczema, urticaria, migraine

4 A family history of allergy

The physical examination during a symptom free period is not helpful, but a high eosinophile count will emphasize the probability of an existing hypersensitiveness—the fifth characteristic of the allergic state<sup>1</sup>

While such data, when obtained, are strongly suggestive of the nature of the disease, there is another phase to be considered in the diagnosis, viz the "exciting factor"

Reference has already been made to the hereditary nature of the fundamental disturbances which permits of the establishment of sensitization in man The acquisition, however, of the specific sensitivity is not governed by heredity, but by the mere chance of exposure to a variety of substances which, when inhaled or ingested, tend to sensitize the susceptible in

dividual Subsequent exposure to the specific substance may result in asthma or hay fever Hence the history of the case must also deal with the influence of occupation, location, environment and seasonal variations on the patient's symptoms Examples of these are to be found in bakers who are sensitive to flour, in grooms who are sensitive to horse dander, in druggists who sneeze or wheeze from the inhalation of lycopodium or acacia, in the hay feverite who suffers only during the pollination season and in the traveling man who loses his symptoms when he sleeps away from home, thus escaping from some environmental dust In other cases the exciting factor is not so obvious and here an exhaustive survey of the case, which may be completed only during several visits and only with the cooperation of an observing patient, is most important A few examples will be illustrative

**Case I.**—A thirty-five-year-old woman residing some 60 miles out of town came in with a history of seasonal "hay fever" and asthma of several years' duration, lasting from June to the end of September The history was suggestive of pollen disease, since her symptoms concurred with the pollination period of grasses and ragweed (N E states) Skin tests with all the indicated pollens proved negative On further questioning it was discovered that the second floor of her house, which was not occupied during the winter, was used for the accommodation of tourists during the summer months Her symptoms began the early part of June, as soon as she started cleaning the upper floor, and ceased about the end of September, when the influx of tourists ceased and the upper floor was closed again On a subsequent visit tests were done with extracts from samples of floor dust and bedding from the upper floor and huge reactions were obtained to most of them By avoiding the upper floor, this patient remained symptom-free throughout the past summer In this case without a history, the causative agent would have been missed and treatment, therefore, unsatisfactory

**Case II.**—A farmer, aged twenty-eight, came in complaining of perennial asthma with aggravation of symptoms from the middle of August to frost. He knew he was "sensitive to horses" but his asthma persisted even when some distance away from the stable Skin tests were positive for horse dander and also for ragweed The latter probably accounted for the aggravation of his symptoms during the fall On further questioning it was discovered that his asthma was also worse whenever he fed the cows Skin tests with cow dander were negative but he gave a striking reaction to an extract of cow fodder He then remarked that whenever he spilled the fodder out of the bag he would choke up badly, but he attributed this aggravation of symptoms to effort Any other effort, however, failed to aggravate his asthma to the same extent He has avoided contact with cow fodder and his asthma has improved since Here again, no progress could have been made without a complete history

**Case III.**—A girl of seventeen was brought in because of perennial "hay fever" of one year's duration Skin tests with the most likely offending proteins

were negative. On further questioning we learned that the patient moved to her present residence some eighteen months ago. In back of her house was a leather finishing establishment where in the process of shaving or "skiving" a lot of leather dust was created. The landlord who lived on the lower floor of the house was also the owner of the leather shop and invariably upon return home from work, would shake his clothes in the corridor thus disseminating the leather dust throughout the house. At my request, a sample of the leather dust was brought in and extracted but when tested on the patient's skin it failed to produce a reaction. Intranasal tests were then resorted to and when a pledget of cotton soaked in the leather extract was inserted into the patient's nose, her "hay fever" was reproduced within ten minutes. None of the controls gave evidence of any such reaction. Subsequently the patient remembered that on a prolonged visit to her uncle some 40 miles away she was symptom free and that upon return home her symptoms recurred. Needless to say that the history alone led to a correct diagnosis, which, after all, is the backbone of successful treatment.

When we consider the countless substances to which one is exposed in his daily life at home and occupation, and that each substance under suitable conditions can become a sensitizer, one appreciates the difficulty of "spotting" every possible exciting factor. Fortunately, however, experience has taught us that in the majority of cases the exciting cause of the disease is to be found in the patient's immediate environment and in his usual dietary and within this sphere our efforts should be expanded, always of course, bearing in mind broader and more distant possibilities. While the search for the exciting factor is often determined through the history of the case alone, in many instances it may be facilitated by the application of the protein sensitization tests.

#### TESTS FOR HYPERSENSITIVENESS

**The Direct Method.<sup>2</sup>**—The mechanism of the "protein" sensitization test is based upon the reaction which takes place when the specific substance or allergen meets its corresponding specific antibody or reagin. In the case of hay fever or asthma, a similar reaction takes place in the nasal or bronchial mucosa, where it causes edema, and in the smooth muscles of the bronchi, which are thrown into spasm. The most logical method, therefore, of testing for hypersensitiveness, would consist of bringing the suspected substance, or an extract of it, in direct contact with the sensitized tissue, and the resulting reaction observed. This is exactly what was done in the leather-sensitive case described above. There are several dis



advantages, however, attached to this direct method of testing

1 The technic is difficult, especially when it comes to introduce the suspected substance into the bronchial tree

2 One is never certain of the extent of the patient's tolerance for the specific substance and an overdose instilled into the bronchi may result in a severe reaction, even to the point of endangering life

3 Not more than one or two tests can be done during a single visit

And yet the direct method of testing proves useful when no reactions to the suspected substance can be obtained by any other methods To illustrate further

**Case IV**—Miss S D has had a persistent cough accompanied by tightness in the chest, of about one year's duration The history suggested hypersensitiveness as the basis for her trouble Skin tests with the routine proteins were negative Further questioning indicated that orris powder might have been the important offender This the patient was loath to believe, especially in the absence of a positive skin reaction to orris I then asked her to lend me her powder compact and submitted myself to the inhalation of a thick powder dust created by shaking the puff Miss D, impressed by the harmlessness of the procedure, submitted herself to a similar exposure with the result that a most distressing attack of cough and asthma followed within a few minutes The patient, convinced of the effect of powder on her bronchial tree, has given up its use and was "cured" (How simple the treatment can be at times!)

Such a procedure, though drastic, is often needed to prove the point What is true of orris powder is also true of most any sensitizing substance which can be instilled or insufflated into the patient's nose or bronchial tree Fortunately, the direct method of testing is not often indicated

**The Skin Test** is usually satisfactory In most instances the patient's skin is involved in the process of sensitization, so that when the suspected protein, in solution, is applied to the scarified skin, a local reaction occurs with whealing, erythema and itching, thus resulting in the so-called "positive" *scratch test*

When is a skin test positive? Generally a skin test is positive only in relation to other negative tests A wheal of from 3 to 5 mm with a surrounding erythema of 8 to 10 mm is positive if all other tested sites fail to react at all On the

other hand, if one or two substances produce a wheal of 10 to 15 mm with a surrounding erythema of 20 to 40 mm, the smaller reactions are only suggestive. Finally, the skin may be irritable and all tests, including the saline control, may react. In such case they are all negative.

Of late this protein skin test has been widely exploited, without due regard to the fact that a positive skin reaction is not always indicative of the cause of the patient's trouble, while at the same time some other nonreacting protein may be at fault. Recent studies<sup>2</sup> have indicated that in asthma 40 per cent of the skin reacting proteins and in perennial hay fever (or vasomotor rhinitis) only 25 per cent are accountable for the patient's symptoms. In seasonal hay fever, the positive skin reactions are accurate in close to 100 per cent. These observations should discourage one from laying too much stress on the skin test alone, but rather utilize it as an adjunct in determining the specific cause of the patient's symptoms.

When by the simple scratch method we fail to obtain a positive reaction to the suspected substance, we may resort to the more delicate *intradermal method of testing*. This is done by injecting the specific extract\* in suitable quantity and concentration between the layers of the patient's skin. When positive, a characteristic local reaction with whealing and erythema occurs. While the intradermal method of testing is more "sensitive" than the scratch method, it is also more irritable to the skin and may be productive of many false reactions. Hence its use should be limited to those cases whose "scratch tests" are negative.

Incidentally, a practical and simple method of skin testing consists of soaking the suspected agent in decinormal sodium hydroxide and applying it, *in toto*, to the patient's scarified skin, preferably on the back.<sup>4</sup> Positive reactions may thus be obtained to a variety of environmental substances, such as rug dust, stuffings from bedding, furniture, etc., and subsequently their clinical importance determined.

The ophthalmic test,<sup>5</sup> the passive transfer of Prausnitz and Kustner,<sup>6</sup> the Leucopenic index of Vaughan<sup>6</sup> and the homely method of trial and error, are additional tests for hypersensi-

\* Protein extracts for intradermal use may be obtained from several biological houses.

tiveness Elimination diets will be referred to again, but space does not permit the discussion of other tests in detail

The question often arises as to how many proteins should a patient be tested with?\* The commercial houses put out over 400 protein extracts, altogether too many for the average case And yet, when one considers the countless substances to which a patient may become sensitized, 400 are too few Hence, the question should be put what proteins should a patient be tested with? The answer to this is in the history of the case Take an account of the patient's occupation, home environment, dietary and the season when his symptoms occur, and then test him with the indicated proteins Sixty to 80 food substances more than cover the average dietary But if the history brings out the patient's fondness for duck eggs and turtle soup, test him also with these two foods Tests with 10 to 15 household allergens are ample for the average case, but if the patient happens to be a chemist and gets his attacks only when in the laboratory, test him with all the chemicals to which he is exposed In pollen sensitive cases, skin tests should be done with the prevailing pollens of a given locality, a familiarity with which is essential Generally, one is to remember that the trees pollinate in the spring of the year (March to June), the grasses during the summer months (June and July) and the weeds during the fall (August and September)

#### OTHER ETIOLOGIC CONSIDERATIONS

While in the main hay fever and asthma may be looked upon as manifestations of human hypersensitiveness, there are instances where such a background cannot be demonstrated Here a family history of allergy may be lacking and skin tests may all be negative The symptoms are generally referable to some reflex irritation or to infection Reflex asthma may be produced through irritation of the sphenopalatine ganglion (asthmogenic area) in the nose or through a pan sinusitis or through stimulation of the vagus through any of its numerous branches, such as cardiac or intestinal It is generally accepted, however, that reflex symptoms occur only

\* See Appendix I

in such individuals in whom hay fever or asthma has been previously established through some specific cause

The rôle of infection in the causation of hay fever and asthma is important though its *modus operandi* is speculative. Some observers uphold the view that infective vasomotor rhinitis and infective asthma<sup>7</sup> are distinct clinical entities wherein bacteria first act as sensitizers and subsequently upon reinfection, as exciting allergenes. Others maintain that bacterial infections lower the threshold of the patient's tolerance for some extrinsic allergen which only then becomes operative and provokes symptoms. Clinical examples which uphold the latter view are numerous. Thus a cat-sensitive patient may be free of symptoms except in the course of a cold, when asthma would set in. A similar cold, in the absence of the cat, does not provoke any asthma. Here infection acts as a nonspecific or as an intermediary cause, which, nevertheless, must be reckoned with seriously, for it stresses the importance of intermediary factors in the causation of respiratory allergy in general. Anything that upsets the patient's physical or mental equilibrium may act as such an agent. On these grounds it is thought that such diverse causes as indigestion, pregnancy, fatigue, constipation, endocrine and metabolic disturbances and even emotional strain, may provoke characteristic symptoms of hay fever or asthma in the susceptible individual. Once a relationship has been established between fatigue and asthma, constipation and asthma, colds and asthma, etc., the symptoms may recur either through a toxic irritation of the neurocirculatory system or on the basis of conditioned reflexes,<sup>8</sup> unless the chain of continuity is broken. Aside from the fact that intermediary agents are capable of provoking symptoms, they often become real complications of hay fever and asthma. Especially is this true of infection. Whether bacterial infection acts as a direct specific cause or as an indirect intermediary cause, sooner or later it tends to dominate the picture in the form of chronic sinusitis, bronchitis or bronchiectasis. As a result of chronic infection, definite and irreversible tissue changes take place in the nose or bronchi, so that symptoms may continue even though the primary exciting cause has been eliminated. Most obvious are these changes in the chronic asthmatics, where advanced

emphysema and secondary cardiac complications dominate the picture. This group of patients taxes the ingenuity of all of us and contributes considerably to our failures.

### TREATMENT

As pointed out in the introduction to this communication, our aim in the treatment of hay fever and asthma is to modify the hypersensitive state clinically. We shall now consider the various measures by which this can be accomplished.

**Relief of Symptoms** —The most important remedy at our disposal is adrenalin. It is a sympathetic stimulator and tends to produce vasoconstriction and to overcome bronchial spasm. Three to 8 minims injected subcutaneously or 1 to 2 minims, intradermally, will relieve asthma of average severity and will influence favorably an attack of hay fever. If no relief follows, the dose may be repeated within twenty to thirty minutes. When no response follows repeated subcutaneous doses of adrenalin, the needle may be inserted into the cubital vein and kept there while 1 minim of adrenalin chloride 1:1000 dilution is injected directly into the circulation at three to five minute intervals, until relief is obtained. This may be followed by  $\frac{1}{12}$  grain of morphine sulphate or a corresponding dose of pantopon, to secure mental relaxation and a prolonged effect of adrenalin. While large doses of morphine are contraindicated in asthma because of their depressant effect on the respiratory center, small doses ( $\frac{1}{12}$  or  $\frac{1}{16}$  grain) are indispensable and where all other measures fail, morphine sulphate, judiciously used, is often the remedy of choice. Not infrequently hypersensitiveness to morphine exists and this is the one serious contraindication to its use. Whereas an attack of hay fever can always be relieved with the aid of adrenalin, ephedrine, morphine and atrophine, asthma occasionally becomes intractable and may persist in spite of all efforts at relief. Such cases, though infrequent in occurrence, are so important and trying that at a recent meeting of the Society for the Study of Asthma and Allied Conditions, the management of intractable asthma<sup>9</sup> was freely discussed from the floor. The following measures were suggested as worthy of trial in any individual case.

- 1 Phenobarbital sodium, 2 grains, subcutaneously
- 2 Subcutaneous normal saline (in a case of intractable asthma with persistent vomiting)
- 3 Colonic administration of ether in oil (patient in collapse)
- 4 Sedation in addition to adrenalin
- 5 Oxygen tent
- 6 Sodium amytal, intravenously
- 7 Caffeine sodium benzoate, subcutaneously in  $7\frac{1}{2}$  grain ampules, every fifteen minutes for 3 to 4 doses, or caffeine citrate, 5 to 7 grain doses by mouth
- 8 Apomorphine,  $\frac{1}{120}$  grain with 1 to 2 grains of codeine and 8 to 10 minims of adrenalin made up together and one third of this administered every five to ten minutes
- 9 Sodium iodide (31 grains) intravenously
- 10 Morphine and atropine
- 11 Two to 3 ounces of whiskey several times a day if needed

mixture consisting of three parts of adrenalin and one part glycerin, altogether 2 cc when injected subcutaneously (with a  $1\frac{1}{4}$  inch 25 gauge needle) will give a less rapid but more prolonged adrenalin effect (The addition of  $\frac{1}{4}$  of 1 per cent nupercain relieves the pain caused by the injection of glycerin-adrenalin) In fact, I have often given 1 or 2 minims of adrenalin intracutaneously for immediate relief and followed this by 2 cc of glycerin-adrenalin for its prolonged effect The chief disadvantage of this method lies in the painful local irritation produced by the glycerin fraction

The inhalation of adrenalin chloride 1 100 concentration for the relief of an asthmatic attack has recently been described by Rowe The author recommends a specially constructed whole glass nebulizer for this purpose\* A very gratifying feature of this method is that the patients obtain relief without the immediate aid of a physician and without the use of a hypodermic needle and long before the full physiologic effect of adrenalin on the circulation, such as tremor, palpitation and pallor, becomes evident

**Ephedrine**—This drug is quite similar to adrenalin in its physiologic effect, though slower in action It is effective when given orally in  $\frac{3}{8}$  or  $\frac{3}{4}$  grain doses When used alone or in conjunction with potassium iodide it is of greatest benefit in the subacute type of asthma A dose of ephedrine taken in time will often abort a threatening attack In hay fever, ephedrine is useful when taken orally or applied locally in the form of a spray or jelly Ephedrine when taken internally may cause restlessness, tremor, sleeplessness and occasionally painful urination in the male These effects may be partly overcome by combining ephedrine with some sedative Ephetonin,<sup>10</sup> a synthetic ephedrine preparation, is said to be less toxic, though fully as efficient A volatile synthetic ephedrine preparation marketed as Benzedrine Inhalant will often palliate an attack of sneezing, though it is ineffective in asthma

Hypertension, when it occurs in asthma, is no contraindication to the use of either adrenalin or ephedrine In fact, with the relaxation of bronchospasm, the blood pressure tends to fall

\* The atomizer may be obtained from the Peralta Hospital, Oakland, Calif

Of the older remedies which still maintain their traditional importance in the treatment of asthma, are stramonium, chiefly in the form of asthma powder, and the iodides. While the former is used mainly in aborting an acute attack of asthma, the latter are more useful in the subacute or chronic stages. The action of iodide is probably systemic as well as local on the bronchial mucosa. Ten minims of the standard solution of potassium or sodium iodide will ease expectoration and reduce dyspnea in a great majority of cases. Although the iodides are readily absorbed through the intestinal tract, they sometimes exert a more beneficial and more rapid effect when administered intravenously. For this purpose sodium iodide in 2 Gm doses (20 cc. ampule) is available commercially. One, two or even three ampules may be administered within twenty-four hours in stubborn cases.

When the acute attack is over the patient may become either entirely symptom free and need no further treatment or the presence of chronic bronchial or sinus difficulty may become evident. In either case an exhaustive physical examination including rhinologic, cytologic, roentgenologic and urinary studies are important. An existing pansinusitis, whether it complicates hay fever or asthma, needs surgical interference. The principle underlying such treatment is the removal of diseased tissue and the establishment of ample drainage. In no way, however, must such treatment be aimed at the relief of the underlying disturbance, although incidentally, the patient's outlook for an "ultimate cure" is better in the presence of healthy nasal chambers. In this regard, Weille's studies<sup>11</sup> are interesting. Out of a group of 40 asthmatics operated on for pansinusitis, only 12 per cent have had complete relief of symptoms for variable periods of time.

x Ray examination of the chest will exclude a coexisting tuberculosis, large tracheobronchial glands, pleural effusions, pulmonary tumors, foreign bodies in the bronchi, all of which may tend to complicate the asthmatic state. Most important of all are bronchiectasis and atelectasis, which constitute the most common and most serious complications of asthma. The former is due to bacterial infection, which thrives well in the poorly aerated peripheral bronchial bed, while the latter is due to the plugging of a bronchus with thick mucous secretions.



causing collapse of the corresponding portion of the lung. On reexamining patients with chronic asthma, one often notes an absence of breath sounds over a given lung area, which may "clear" suddenly after a coughing spell or within twenty-four hours. At the same time another portion of the lung may become atelectatic.

For the relief of bronchiectasis complicating asthma, postural drainage is the measure of choice. The patient leans over the bed, his hands reaching the floor, and forces himself to cough for a period of three to five minutes. The procedure should be repeated two or three times a day and continued for months. While "cure" is out of the question, relief of symptoms with diminution in the amount of sputum are common following this procedure. Ammonium chloride, T I D in 3 grain doses, will help to liquify the sputum. Recently<sup>12</sup> postural drainage has been suggested in all asthmatic patients on the basis of relieving the "accompanying bronchial and pulmonary exudate."

For atelectasis, the treatment of choice is removal of the plug of mucus through a bronchoscope. This procedure, though unpleasant for the patient, is not dangerous, and is often extremely helpful. Such treatment, however, should not be used promiscuously. The patients should be carefully selected and at the same time should be subjected to a bronchography with lipiodol for further diagnostic details. In fact, repeated lipiodol instillations without bronchoscopic drainage have been suggested as a therapeutic measure in infected asthma. This is not, however, an accepted method of treatment.

Cytologic and urinary examinations may divulge a co-existing blood dyscrasia or a kidney affection, the correction of which will enhance the possibility for better results in the management of asthma or hay fever.

The status of the "heart in asthma"<sup>13</sup> is still clouded with uncertainty. Logically, the right chamber should suffer because of the increased resistance to the pulmonary circulation in asthma and its frequent concomitant emphysema. x-Ray and electrocardiographic studies, however, fail to substantiate such an assumption. As to dyspnea on effort, the most important symptom of cardiac embarrassment, this is so obscured

by the pulmonary dyspnea incident to the asthmatic state, that the two cannot be differentiated. And yet, a daily dose of  $1\frac{1}{2}$  to 3 grains of digitalis in the older patient with asthma, with feeble and rapid pulse, may be of some benefit. Cardiac irregularities, when they occur, must be treated without regard to the coexisting asthma.

**The Treatment of the Exciting Cause**—The next step in the treatment of hay fever and asthma is concerned with an allergic survey of the patient. Reference has already been made to the importance of the history in determining the nature of the exciting factor. In this regard, the patient's environment, occupation and dietary have been particularly stressed as the most common sources of trouble. A critical analysis of the skin test has been briefly presented. When neither the history of the case nor the skin tests prove helpful in determining the nature of the exciting factor, the following measures may be resorted to both for diagnostic and therapeutic purposes.

1 *Change of Environment*—To this end, hospitalization is the procedure of choice. In the absence of such facilities, a change to a friend's or relative's home for a week or two may be helpful. Sometimes a change to a different bedroom, even in the same house, may bring about gratifying results. Relief thus obtained points to the environment as the source of trouble. Upon reentering his home, however, the patient's symptoms may recur. Hence a systematic course of "allergic cleanliness" should be instituted before allowing the patient to reenter his old habitation.

2 *Allergic Cleanliness*—Allergic cleanliness differs from general "household cleanliness" in that the latter is directed toward the removal of dust, while the former is aimed at the elimination of its source. Experience has taught us that bedding, overstuffed furniture and rugs are the most common sources of active household allergens. Hence the mattresses and pillows should be either changed or encased in rubberized dust impermeable cloth, while comforters should be substituted by freshly washed blankets. Recently a liquid rubber (*Vultex*\*)<sup>14</sup> has been suggested as an efficient agent for protecting pillow and mattress against dust emanation. A coating

\*Vultex Chemical Company 660 Main Street, Cambridge Massachusetts.

of Vultex is applied with an ordinary brush and allowed to dry overnight. This seals the bedding and makes it dust proof. Rugs and overstuffed furniture should be removed from the patient's bedroom. Closets are dust collectors, hence they should be whitewashed and only freshly cleansed clothing be kept there. Furnace registers are apt to bring in a good amount of cellar dust, hence they should be covered with muslin, which acts as a partial filter. Perfumes, powders, disinfectants, deodorants, moth-killing sprays, are common offenders and should not be permitted in the patient's room. Whatever is washable, such as curtains, draperies, bedspreads, may be left in the room with impunity.

The living room furniture, next in importance, as a dust producer, cannot be handled with the same ease as the bedding. Efforts should be made to obtain samples of stuffing from the divan, chairs, rugs, etc., and each sample should be soaked in decinormal sodium hydroxide and tested on the patient's skin. In the presence of a positive reaction, the stuffing should be changed or the furniture eliminated. When this is impossible, the patient should remain in his own room for comfort. Sun parlor furniture and overstuffed scatter chairs are all possible sources of trouble and should be handled in like manner.

The kitchen is usually least troublesome of all rooms, except for the presence of dusting powders and baking powders, which may be offensive to the patient. Usually, however, the patient is conscious of the ill effects of such products and tries to avoid them. A mouth and nose mask, consisting of 10 layers of gauze and worn while dusting or washing, will act as an efficient filter.

The bathroom should be kept clear of powder and perfumed soaps. Tooth powders and pastes often contain orris root, a common offender, hence, it is my practice to substitute these with common table salt for a trial period.

These measures, in brief, constitute "allergic cleanliness."

3 *Elimination Diets*—Rowe's elimination diet<sup>16</sup> may be instituted at the same time with allergic cleanliness. A trial period of seven to ten days is ample to determine the effects of each diet on the patient's symptoms. If no relief is obtained within that period, foods are not likely offenders. An-

other form of trial diet consists of limiting the patient to one type of food, such as milk, for a period of three to five days. If improvement follows, additional foods are given each subsequent day, until the "offender" is determined. Where sensitivity to milk is suspected, beef broth or thin gruel with maple syrup may serve as the initial food. (See appendage II.)

**Desensitization.**—In a good many cases the exciting allergen is elusive, in others, though found, it cannot be eliminated, as often is the case in pollen-sensitive patients or in the occupational allergies. In such instances we must resort to the *third method of treatment*, viz. an attempt to change the reactivity of the patient's tissues by desensitization. Desensitization may be *specific*, when the treatment is carried out with an extract of the offending substance, or it may be *nonspecific* when any shock producing agent, such as milk, pepton or tuberculin is injected into the patient parenterally.

**Specific Desensitization.**—Any substance which is causative of the patient's symptoms and which produces a positive skin reaction, can be utilized for specific desensitization. The first step in desensitization is to establish the extent of the patient's tolerance for the indicated allergen. In the case of pollens, a concentration of 1:50 can be purchased from any of the several commercial houses and dilutions of 1:500, 1:5000, and 1:25,000, prepared with saline under sterile conditions. Some biological houses offer the pollens already prepared in the various dilutions. The patient's forearm is then cleansed with alcohol and a drop from each of the pollen dilutions is placed over its anterior surface. Using a fine scalpel or the sharp point of a needle, each site is gently scarified, always starting with the weaker dilution and working up to the most concentrated one. Within twenty to thirty minutes a characteristic reaction with whealing pseudopod formation and surrounding erythema will appear. The more concentrated the extract, the stronger the reaction, so that the weaker dilutions of 1:5000 or 1:25,000 may fail to react at all. Treatment is then instituted with that dilution which fails to produce any appreciable reaction. 0.10 cc. of such a dilution is a safe initial dose. If the local reaction from the first dose does not exceed the size of a silver dollar, it is safe

to increase the following dose by 0.10 cc. And so each subsequent dose is estimated by the extent of local reaction from the preceding one. An extensive swelling at the site of injection always calls for a repetition or even a diminution of the previous dose. The change from a weaker to a stronger dilution must be exercised with a great deal of care and caution. While there are no fixed rules for this procedure, the following suggestions may be accepted as a working basis.

If the last dose is 0.4 cc. of 1:25,000 dilution, the next dose may be 0.1 cc. of 1:5000 dilution.

If the last dose is 0.9 cc. of 1:5000 dilution, the next dose may be 0.1 cc. of 1:500 dilution.

If the last dose is 0.9 cc. of 1:500 dilution, the next dose may be 0.1 cc. of 1:50 dilution.

As to the number of doses needed in each case, no one can venture to guess, for each patient is a "case unto himself" and his needs are determined by the severity of his symptoms, by the average concentration of pollens in his district and above all by his inherent response to treatment. The first year of pollen treatment is the trial period and the patient should be informed about this at the outset, so that a poor result may not reflect unfavorably on the physician nor on the method employed in treatment.

The aim in pollen therapy, and for that matter in all therapy by desensitization, is to raise the patient's tolerance for the given allergen, to a maximum. In one case it may take 10 pollen doses, while in another 50 pollen doses, to accomplish the same results, moreover, the final or optimal dose may in one instance be 0.1 cc. of 1:500 dilution, while in another a whole cubic centimeter of 1:50 concentration. Hence, it is fallacious to undertake such therapy with any performed schedule of "doses."<sup>16</sup> One must "feel his way in the dark" and forge ahead cautiously and wait for the appearance of the pollen season to decide on the efficacy of the treatment. Granted that the patient has been brought up to his maximum level, that attempts to further increase the dosage meet with obstinate resistance in the form of large local reactions or even constitutional reactions, does it mean that the patient will have desired relief the coming season? In a large percentage of cases, yes, but in the others relief may be slight or nil. It

is these poor results in pollen therapy that bother us a lot, and so far no one has ventured a final word as to their cause. It is generally accepted, however, that failure in pollen therapy may be due to insufficient treatment, to the existence of additional sensitivities, to structural intranasal abnormalities, to coexisting nutritional disturbances or to an inherent refractoriness of the tissues to therapy. A search for all such factors, and where possible, their elimination or correction may bring about better therapeutic results in the future. At all times, however, it is well to bear in mind that desensitization in man is a *relative* and not an *absolute* procedure and that a heavy pollen season invariably means a larger number of poor results.

There are four generally accepted methods of desensitization. We shall consider them in order of their importance.

1 *Preseasonal Method*—Here the treatment is instituted four to six months before the expected date of pollination and doses are given at weekly intervals. With the onset of the season, the last dose may be decreased one third and repeated at seven to ten day intervals to the end of the season. If a patient proves resistant to treatment, smaller but more frequent doses may be given at three to four day intervals. An overdose after the onset of the season may precipitate severe and persistent hay fever.

2 *Perennial Method*<sup>17</sup>—At the completion of a season's treatment, the final dose may be maintained throughout the following nine months at four-week intervals. By this time, a change to fresh pollen extracts will necessitate a diminution in dose and from then on the treatment is again continued with increasing doses to the point of maximum tolerance. Not all patients, however, so treated can maintain a fixed tolerance so that after the third or fourth month the local reactions may become large and consequently the dose has to be reduced. After two or three years of perennial treatment, a fairly stabilized tolerance for a higher concentration of the pollens becomes established and only at this time are the results almost invariably satisfactory. A serious disadvantage of this method is the need of constant visits to the doctor throughout the year, which is often depressing to the patient.

3 *Coseasonal Method*—This is applicable in those cases

who first come for treatment after the onset of symptoms. Here, the daily administration of small doses of pollen extract with the addition of 0.25 cc of stock catarrhal vaccine every fourth or fifth day is apt to give the patient some relief. Again it should be remembered that an overdose at this time may precipitate most severe and lasting symptoms.

4 *The Rush Method*<sup>18</sup>—A few days before the expected date of pollination the patient is placed in the hospital under close supervision and is given small though increasing doses of pollen at one or two hour intervals. This procedure is repeated for several days and the patient discharged. Though good therapeutic results are claimed for this method, the rapid cumulative effect of the pollens with a possible resultant constitutional reaction nullify its advantages.

Constitutional reactions are best treated by preventing them. This can be accomplished by carefully estimating the indicated dose and by avoiding the injection of pollen directly into the circulation. When it occurs, the constitutional reaction is combated by placing a tourniquet *above* the site of inoculation and by administering adrenalin in sufficiently large doses to overcome the symptoms. I have found that a tight elastic placed above the point of inoculation will retard the absorption of pollens and lessen the tendency to constitutional reactions. This is particularly indicated in patients who are highly sensitive to pollens.

Whatever has been said in regard to pollen therapy is equally applicable to the use of any other allergenic extract for desensitization in either hay fever or asthma. Since the allergenic potency in some substances is more active than in others, it is important to carry the dilutions high enough even to 1,000,000, in order to obtain a safe initial dose for therapy.

**Nonspecific Desensitization**—Any substance which, when injected parenterally, produces a general reaction in the body, tends to alter the reactivity of the tissues to specific irritants. While the mechanism here involved may actually stimulate the immune processes in the body it is, nevertheless, nonspecific in that the therapeutic results are related not to the substance injected, but to the reaction it produces. Thus, milk, blood serum, whole blood, pepton, sulphur in oil, tuber-

culin and vaccines are commonly used for the production of such reactions. Although the response to such treatment in hay fever and asthma is variable, the procedure is nevertheless justifiable, when other measures fail to produce results. Of the several shock substances suggested for use, milk in 10 cc doses, 1 to 5 per cent pepton in 1 cc. doses and whole blood withdrawn from the patient's cubital vein and reinjected into the buttocks in 10 cc doses, are commonly employed. Intravenous injections of all such substances should be guarded against.

Vaccines are the most valuable nonspecific measures. Rackemann's<sup>19</sup> tenets for vaccine therapy "no reactions, no results," whether one uses autogenous or stock vaccines, still hold good. In our hands tuberculin has not proved advantageous over other types of vaccine. A good stock catarrhal vaccine will usually serve the purpose. In administering vaccines it is well to start with a small dose of 0.25 cc. and increase it by 0.1 cc. at four to seven-day intervals. One always aims to obtain a local reaction the size of a silver dollar. Occasionally we see a patient who is sensitive to bacterial proteins and whose asthma becomes aggravated within two to twelve hours after the injection of vaccine. In such instances the vaccine should be diluted with saline 1:100 and treatment instituted with 0.1 cc. of this dilution. At all times should the dose be kept below its injurious level. Reports in the literature on the particular advantages of autogenous vaccines are not lacking (Thomas-Asthma),<sup>20</sup> but in many trials we have never been able to substantiate such claims and an extensive experience shows results with stock vaccines quite the same as those with autogenous.

**Oral Desensitization.**—When a sensitivity to the ingestion of certain foods is responsible for hay fever or asthma, desensitization by the subcutaneous method is ineffective. Here oral desensitization may be tried. The technic of oral desensitization is as follows: 1 drop of the offending food (egg white or milk) is diluted in 1 quart of water and a teaspoon of the mixture is taken three times a day, after meals. If no ill effects follow, the same amount of food is diluted in a pint of water and again three teaspoons taken a day. The quantity of diluent is gradually decreased from day to day.



until it consists of only one ounce of water. From then on the quantity of food is increased instead of diminishing the amount of diluent. Thus we add 2, 3, 4, 5 drops of the food to the ounce of water until the patient is able to take the whole food with impunity. Theoretically this method works out better than practically, but at the same time it is worthy of trial. Nonspecific oral desensitization as had been advocated by Urbach,<sup>21, 22</sup> at first with heterogenous and later on with homologous propeptons have not created sufficient enthusiasm in this country to deserve unreserved recommendation.

### OTHER METHODS OF TREATMENT

Satisfactory results in the treatment of hay fever and asthma with viosterol in high concentration (10,000 units) have been reported by Rappaport<sup>23</sup> *et al*. Commencing about ten days before the expected date of pollination, 4 to 10 drops of the drug are administered daily. Where tolerance permits, the dose may be increased up to 60 minims a day. When treatment with viosterol was combined with specific desensitization the end-results were more satisfactory. The treatment of asthma with hormones of the adrenal cortex and sodium chloride as recently proposed by Pottenger,<sup>24</sup> *et al*, offers a direct approach to the host on the basis of a hormone deficiency. We shall be hopefully awaiting further developments of this method. Beckman<sup>25</sup> reports his results on the treatment of hay fever with large doses of hydrochloric acid and finds them comparable to the results obtained from treatment by desensitization. Our own experiences with this method of treatment are scant. The use of nose and mouth masks is often indicated in the occupational allergies, such as in bakers who are sensitive to flour and who fail to obtain palliation through specific desensitization. Such masks, though cumbersome and conspicuous looking, enable the patient to gain some comfort at his work. Air conditioning<sup>26</sup> in pollen disease is helpful, at least as long as the patient remains in the air-filtered room. Upon leaving the room, however, the symptoms recur. Hence, air conditioning should be used only as an adjunct to, but not as a substitute for, specific desensitization.

Nasal ionization for the treatment of vasomotor rhinitis as proposed by Warwick,<sup>27</sup> has received considerable attention of late. This method is still new and though apparently productive of immediate relief in about 50 per cent of the cases, its possible injurious effect on the nasal mucosa<sup>28</sup> calls for rational conservatism.

### SUMMARY

In retrospect, the question may arise as to what constitutes the recent advances in the treatment of hay fever and asthma? Since Noon and Freman's introduction of specific therapy in pollen disease and the subsequent application of this method to other forms of vasomotor rhinitis and of asthma, there has been but little progress on this subject. Emphasis, however, has been noted throughout the literature on the fundamentals of allergy and on its chemical and immunologic phases. Only through such broader concepts of the subject is an approach to rational therapy possible. These tendencies are witnessed in Rackemann's<sup>29</sup> recent review on the progress of allergy: out of 372 publications he selected 111 as representative of the best thoughts on the subject. Of these 111 only 4 are given to "treatment," while the others deal with the various phases of allergy at large. And yet, clinical experience tends to crystallize the adaptation of current therapeutic measures and these we have attempted to stress in this communication. One other fact is worthy of comment. The allergic concept of asthma and hay fever has sent into oblivion some of the older measures of which physicians, in the preallergic era, availed themselves. Amongst these, balneotherapy, physiotherapy, hydrotherapy, general tonic measures, were most noteworthy. So thoroughly have all these been forgotten, that their consideration anew might justly be included in the "Recent Advances." But the subject is vast and would in itself form an important communication.

### APPENDIX I

A suggestive list of foods and inhalants for use in routine skin testing of patients. This list should be supplemented by such other proteins as may be indicated from the history of the case.

*Foods*

| <i>Cereals</i> | <i>Meats</i>         | <i>Fish</i> | <i>Shell-fish</i>   | <i>Vegetables</i> |
|----------------|----------------------|-------------|---------------------|-------------------|
| wheat          | beef                 | haddock     | crab                | potato            |
| rye            | veal                 | halibut     | lobster             | tomato            |
| barley         | lamb                 | salmon      | oyster              | asparagus         |
| corn           | chicken              | cod         | shrimp              | beet              |
| oats           | pork                 | mackerel    | clam                | cabbage           |
| rice           |                      | flounder    | scallop             | onion             |
| <i>Fruits</i>  | <i>Miscellaneous</i> | <i>Nuts</i> | <i>Egg and milk</i> | carrot            |
| apple          | cinnamon             | almond      | egg white           | kidney bean       |
| pineapple      | poppyseed            | walnut      | egg yolk            | lima bean         |
| banana         | nutmeg               | cocoanut    | milk (cow)          | lettuce           |
| pear           | mustard              |             | lactalbumin         | mushroom          |
| peach          | ginger               |             |                     | sweet potato      |
| plum           | buckwheat            |             |                     |                   |
| orange         |                      |             |                     |                   |
| grapefruit     |                      |             |                     |                   |
| grape          |                      |             |                     |                   |
| olive          |                      |             |                     |                   |
| cheery         |                      |             |                     |                   |
| strawberry     |                      |             |                     |                   |

*Dusts*

| <i>Epidermals</i> | <i>Miscellaneous</i> |
|-------------------|----------------------|
| cat hair          | kapok                |
| dog hair          | cottonseed           |
| cattle hair       | house dust           |
| horse dander      | flaxseed             |
| hog hair          | orris root           |
| feathers          | pyrethrum            |
| chicken           | boxwood              |
| duck              |                      |
| goose             |                      |
| goat hair         |                      |
| sheep wool        |                      |

*Pollens* These vary with different localities. Hence it is essential to establish a familiarity with the important pollen flora, of a given area before undertaking pollen tests. Mr. Durham of the Abbott Laboratories has always been cooperative in rendering such information.

## APPENDIX II

## ROWE'S "ELIMINATION DIETS"

|                                  | <i>Diet No 1</i> | <i>Diet No 2</i> | <i>Diet No 3</i> |
|----------------------------------|------------------|------------------|------------------|
| Cereal                           | rice             | corn             | rice             |
|                                  |                  | tapioca          | rye              |
| Bread                            | rice biscuit     | corn pone        | rye-rice         |
| Meat or Fish                     | lamb             | bacon            | beef             |
|                                  |                  | chicken          |                  |
| Vegetables                       | lettuce          | squash           | tomatoes         |
|                                  | spinach          | asparagus        | beets            |
|                                  | carrots          | peas             | string beans     |
|                                  |                  | artichokes       |                  |
| Fruits and jams and fruit drinks | lemons           | pineapple        | grapefruit       |
|                                  | pears            | apricot          | pears            |
|                                  | peaches          | prunes           | peaches          |
|                                  |                  | sugar            | sugar            |

|               |  |                                       |  |
|---------------|--|---------------------------------------|--|
| Miscellaneous | sugar<br>olive oil<br>salt<br>gelatin<br>syrup                               | Mazola oil<br>salt<br>karo corn syrup | Wesson oil<br>salt<br>gelatin<br>syrup made from cane<br>sugar flavored with<br>maple. |
|               | made<br>from cane<br>sugar flav<br>ored with<br>maple.<br>olives (unstuffed) |                                       |  |

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It is, therefore, wise to consider how much we know about dietetic therapy

We have learned much about the vitamins in recent years. We know that the absence of a vitamin can produce severe diseases which clear up almost miraculously with the introduction of the necessary foodstuff.

The disease known as xerophthalmia responds to the administration of vitamin A, beriberi to vitamin B, scurvy to vitamin C and rickets to vitamin D. Also we have learned much about the nature of these vitamins. Vitamin B has been crystallized and has the chemical form of a hydrochloride of picrolonic acid. C is known to be 1-cevitamic acid and D is a sterol. Hence, these substances are chemical compounds which we believe may act as catalysts, that is, they aid or hasten what otherwise may be an ineffective chemical reaction. Vitamin B seems to influence the oxidation of carbohydrates. Vitamin C has been shown to be a strong reducing agent in the test tube. Vitamin D influences the action of calcium and phosphates in the bones although it is not yet known in what way it does this.

We have also learned much about how the vitamins affect the body and its different systems. Vitamin A influences the epithelial tissues of the body and in its absence the skin tends to become cornified. A reduction of tone and motility of the gastro-intestinal tract and a polyneuritis follows a deficiency in vitamin B. An absence of vitamin C results in a lack of an intercellular cementing substance with a resulting leakage or extravasation of blood into the tissues. Vitamin D aids the absorption of calcium from the intestinal tract and seems to influence the chemistry of calcium and phosphorus within the body.

In addition to these facts, which are now generally accepted, there has been a large amount of information reported from laboratory studies which cannot be dealt with completely at this time and some of which is in dispute. Some workers report that vitamin A specifically stimulates the intestinal mucous membrane and directly or indirectly the formation of blood platelets. An atrophy of the intestinal villi is said to occur in the absence of this vitamin. A lack of vitamin B is said to result in congestion and hemorrhage into the bone

marrow Also it is said to produce an atrophy of lymphoid tissue with a lymphopenia characteristic of nutritional changes

Interesting as these findings may be, the clinician must remember that they are still in the phase of investigation If, for example, a lack of vitamin B produces atrophy of lymphoid tissue and a lymphopenia, it does not follow that the finding of a lymphopenia should necessarily be treated with vitamins

The question of how far we should go in using vitamins is hard to evaluate at the present time Some very good men have advanced the idea that many symptoms may be the result of an insufficient amount of these substances However, we must not forget that a very small amount of a vitamin is required to eradicate completely all vestiges of those conditions like scurvy, which are known to be caused by an inadequate intake of a vitamin Therefore, one should be cautious about attributing other conditions, frequently with indefinite symptoms, to an insufficiency of vitamins, particularly if the patients seem to be taking a normal diet Certainly it is true, that in this period when the population is "vitamin conscious" very few persons take an insufficient quantity The diet of most adult Americans contains enough vitamins to prevent the picture of a severe insufficiency such as occurs in beriberi and scurvy The present free use of vitamin mixtures either with or without a doctor's sanction would seem to preclude an insufficient intake in most patients

Therefore, if indefinite complaints of bodily aches, chronic indigestion, lack of vitality, etc., depend upon a vitamin lack, it is reasonable to believe that in some cases the difficulty may be an inability of the body to utilize the vitamin rather than an inadequate supply

The second patient illustrates another group of diseases which can be relieved by diet.

**Case II**—This thirty six year-old married clerk entered the hospital because of persistent weakness and fatigue of two years duration. The family and past history are irrelevant She felt perfectly well until twenty two months before admission when she caught cold and suffered from headache, malaise, anorexia, weakness and fever She remained in bed for four and a half months after which she began a slow convalescence which was marked by fatigue, dyspnea, palpitation and weakness. By fall she was able to work half a day but with great effort Two months ago she was attacked suddenly by what she described as an "awful dead all gone feeling" Her physician said



she was anemic and advised rest. About three months before entry she began to be troubled with nausea, vomiting and gagging after eating.

Physical examination revealed an emaciated woman with a lemon yellow tint to the skin. The face was drawn. The sclerae were very white. Many flame-shaped hemorrhages were present in both fundi. At the time of entry her hemoglobin was only 15 per cent, red blood count 880,000 and white blood count 3800. The red cells showed marked achromia, anisocytosis, poikilocytosis, normoblasts, polychromatophilia and stippling. No platelets were seen. Following one transfusion and intramuscular injections of liver extract she began to improve. After one month the hemoglobin was 86 per cent, the red blood count was 5,480,000 and the white blood count was 8500. Now she feels perfectly well.

This patient suffers from pernicious anemia, a disease which presents, or at any rate emphasizes, certain problems which scurvy does not. Scurvy develops in a normal person from an inadequate supply of vitamin C, whereas pernicious anemia may occur on a normal diet with an inadequate gastric function. The patient with pernicious anemia develops symptoms because of an inability to manufacture from a normal diet something essential to the body. Therefore, the clinician must remember that there are at least two factors in the study and treatment of deficiency diseases. One is the amount of essential substances available in the diet. The other is the ability of the body to utilize these substances.

With our present limited knowledge of the subject, it is alluring but dangerous to speculate on how many of our medical problems are associated with a deficient state. Pellagra and sprue are two clinical entities which seem closely allied to pernicious anemia. Both are benefited by dietetic treatment. Brewer's yeast and fresh liver are said to be especially rich in the pellagra-preventive substances. Sprue is reported to be relieved by liver extract. Although the three diseases have certain qualities in common they present a sufficiently characteristic picture to make possible a clinical differentiation. We have yet to learn what causes these various pictures. Are they the result of a difference in the utilization of the same foodstuffs, and if so, upon what does the difference in utilization depend? As an evidence of how little we know about this problem is the fact that as late as 1934 one of the standard textbooks retained sprue under the infectious diseases. Our lack of knowledge about this group of diseases emphasizes that we should not expect to cure all patients that

suggest a deficiency by the simple means of giving a normal diet.

Finally, I want to present very briefly this last case for your consideration because it involves the mineral content of the food

**Case III.**—This young boy of ten years was brought into the outdoor department following an automobile accident. He was not hurt seriously, but an x ray was taken of his leg for a possible fracture. The film revealed a healed rickets. The patient is now well but is of interest because he shows evidence of a former illness which was produced by a diet inadequate in vitamin D phosphorus, or both. The case is an example of the importance which diet plays in providing the body with sufficient minerals.

Our knowledge about the effect of minerals on the body has increased rapidly of late. We have learned that certain minerals are essential to the normal functioning of tissues, as for example, iodine in relation to the thyroid, iron to the blood, calcium and phosphorus for the bones.

The salts maintain the reaction of the blood and control the osmotic pressure in the organism. An imbalance in the amount of the various minerals and salts results in widespread systemic effects. Alkalosis is met with not uncommonly from continued loss of chlorides through vomiting and the alkaline treatment of peptic ulcer. Many of the symptoms of heat exhaustion have been traced to an excessive loss of sodium chloride in the sweat.

Our recent knowledge has supplied us with therapeutic triumphs. The treatment of heat exhaustion with sodium chloride is of distinct value. The great contribution to our therapy in lead poisoning came from Aub's study of the behavior of minerals within the body.

More recently it has been reported that an acid base diet is useful in treating patients with renal calculi of a certain type.

We can look forward to further advances in therapy. Further knowledge of the chemical behavior of minerals within the body should open the way for a more efficient treatment of edema. But such advances can only come through the information obtained from careful laboratory studies. Meanwhile the profession must guard against foolish therapy based on inadequate knowledge. It is worth emphasizing that the

amount of minerals which the body requires is small. The normal adult needs roughly 0.015 Gm of iron, 1.32 Gm of phosphorus and 0.68 Gm of calcium per day. Therefore, the actual needs of the body are easily supplied. The profession is facing the same problem that has so often presented itself with any new knowledge. The public will become "mineral conscious," and we can look forward to a wave of injudicious treatment.

Only the discriminating use of our new knowledge by the profession can serve as a brake against foolish therapy and quackeries which always arise at such a time.

## CONTRIBUTION BY DR FREDERICK T LORD

BOSTON

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### CERTAIN ASPECTS OF THE COMMON COLD

LITTLE is known regarding environmental factors as a cause of colds. The hypothesis is presented by Kerr and Lagen<sup>1</sup> that the disease represents a failure of the body to adjust itself to a varying environment, as against an infectious origin. In support of this theory, presumably susceptible subjects under conditions arranged for maximum comfort, failed to develop colds under intimate exposure to individuals in the early stages of the disease or after inoculation with nasal secretion from persons with colds.

The greatly increased incidence of colds during the colder months of the year lends support to atmospheric conditions as a factor. Van Loghem<sup>2</sup> noted that epidemics of colds in Holland follow sharp drops in temperature. Milam and Smilie<sup>3</sup> also found that outbreaks of colds in the tropics coincided with sudden fall in temperature of a few degrees. Paul<sup>4</sup> states that epidemics of colds occurred on the research vessel Carnegie after many days or weeks out of port after the ship entered a cold current from warmer waters.

The investigations of Rossbach,<sup>5</sup> Muller,<sup>6</sup> Miller and Noble<sup>7</sup> and Mudd, Grant and Goldman<sup>8</sup> suggest that chilling of the body surface in animals and man may induce changes favorable to local invasion of the mucous membranes by organisms already present and otherwise harmless.

<sup>1</sup>Tr Assoc Amer Phys., 49 245 1934

<sup>2</sup>Jour Hyg., 28 33 1928-29

Jour Exp Med., 53 733 March 1931

<sup>3</sup>Paul and Freese Amer Jour Hyg., 17 517 May 1933

<sup>4</sup>Berl. klin. Woch., 1887

<sup>5</sup>Deutsche Klinik, 1903-04

<sup>6</sup>Jour Exp Med., 24 223, 1916

<sup>7</sup>Ann Otol., Rhinol. and Laryngol., March 1921

In spite of such observations, there is nothing to support the belief that environmental factors alone are of importance. The great frequency of exposure in wet weather, wet feet, sitting in wet clothes or draughts and rapid cooling when overheated without ill effects is suggestive of little more than a chance relation. It is difficult to estimate the importance of lowered temperature, in view of the tendency in cold weather to live in crowded and poorly ventilated rooms with consequent greater opportunity for spread by contact.

Nansen's often quoted experience of freedom from colds among members of his expedition under exposure to the rigorous climate of the far North is against exposure to cold as a factor. The development of colds and coughs among many of his party when, on their return, they landed at a thickly settled port, is strikingly suggestive of a contagious origin.

The investigation of small isolated communities has apparently established spread of the disease by transmission from person to person. Studies in certain Eskimo settlements (Greenland) by Heinbecker and Irvine-Jones<sup>9</sup> and in Longyear City (Spitzbergen) by Paul and Freese<sup>10</sup> indicate that outbreaks of colds arise from exposure to persons from without and involve a large proportion of the population. Paul and Freese find in a group of 500 persons in Longyear City that colds are largely concentrated into an explosive epidemic following the annual resumption of steamer traffic with Norway. They suggest that the population is too small to permit transfer of the inciting agent from person to person with sufficient frequency to retain its original virulence and give rise to an epidemic during the months of isolation from the outside world.

A filtrable virus was suggested as the cause of colds by the investigations of Kruse<sup>11</sup> and Foster<sup>12</sup>. Dochez and his associates have made additional contributions of great value. They find that anthropoid apes and especially chimpanzees are susceptible and that infection is readily communicated from man to the ape and from one ape to another. The dis-

<sup>9</sup> Jour Immunol, 15 395, 1928

<sup>10</sup> Amer Jour Hyg, 17 517, May, 1933

<sup>11</sup> Münch Med Wchnschr, 61 1547, 1914

<sup>12</sup> Jour Amer Med Assoc, 66 1180, April 15, 1916

ease can be produced in an experimental subject by inoculation with filtered nasal secretion from an individual with a cold, the organism recovered by culture and the disease reproduced by inoculation with the culture material. The inciting agent remains active after many generations of growth in tissue cultures. Production of colds with bacteria-free filtrates excludes the presence of ordinary organisms as a cause. The constituents of the culture material itself and the heated culture of the virus at times produced temporary irritation, but not the manifestations of colds. An origin of colds from infection with a filtrable virus must be regarded as established.

As with other infectious diseases, not all persons appear to be susceptible. Following a cold there is a short period of immunity, the duration of which may be estimated from the observations of Paul and Freese at a minimum of twenty-three days and an average of seven weeks. Dochez's experiments on chimpanzees indicate that resistance to reinfection lasts only about a month. A short period of immunity increases the difficulty of solving the problem of prevention by any method of artificial vaccination.

Investigation of the flora of the nasopharynx under normal conditions and during colds by Dochez and his associates, Burky and Smillie,<sup>13</sup> Kneeland,<sup>14</sup> Milam and Smillie<sup>15</sup> and Paul and Freese<sup>16</sup> suggests that the bacteria harbored in the upper air passages are not to be regarded as the inciting agents of the disease. They play an important part, however, as secondary invaders. The seriousness of a cold is almost entirely due to its tendency to initiate such disturbances of a grave nature as bronchitis, otitis media, sinusitis, bronchopneumonia and lobar pneumonia. Among patients with lobar pneumonia, for example, 76 per cent give a history of a cold within a short period of the onset of pneumonia. Smillie and Caldwell<sup>17</sup> found pneumococci increased in the nasopharynx or persons with acute colds, and Dochez, Mills and Kneeland<sup>18</sup>

<sup>13</sup>Jour. Exp. Med., 50 643 1929

<sup>14</sup>Ibid., 51 617 1930

<sup>15</sup>Ibid., 53 733 1931

<sup>16</sup>Loc. cit.

<sup>17</sup>Jour. Exp. Med., 50 233 Aug., 1929

<sup>18</sup>Proc. Soc. Exp. Biol. and Med., 30 314, Dec., 1932

noted in chimpanzees during the early stages of the cold, whether spontaneous or experimental, a great increase in the numbers and the area of distribution of the common pathogens of the upper air passages, such as the influenza bacillus, pneumococcus and hemolytic streptococcus. Under the influence of infection of the animals with the virus of the common cold, a transformation was observed from the S to the R type of influenza bacillus during the period of the cold, while only R forms could be cultivated during the intervening period. Such observations suggest that one of the most important effects of the virus of the cold is to incite activity on the part of potentially pathogenic micro-organisms present in the nasopharynx at the time of infection.

There is no practical method for the prevention of colds under ordinary conditions of life and none of the numerous measures suggested has been proved to be successful. The difficulty of avoiding contagion is suggested by the observation of Heinbecker and Irvine-Jones<sup>19</sup> that it was not necessary for members of the expedition to have a respiratory infection for the disease to appear among the natives. It is, nevertheless, desirable to attempt to prevent colds in infants, invalids and the aged by the avoidance of known contact and in them special care should be exercised against exposure to rapid changes of temperature. Adequate ventilation, maintenance of an equable temperature within doors and humidification may prevent the development of complications in those who have colds.

On the part of those with colds, for the protection of others, precautions should be taken to prevent droplet and contact infection. It is possible that transfer of bacteria heightened in virulence by the inciting agent of the cold may more readily give rise to infection on transfer to others.

There is no evidence that hardening or toning-up processes, ultraviolet radiation, vitamins or nasal douches are useful in prevention. Vaccination with a mixed vaccine containing killed bacteria ordinarily found in the nasopharynx has not, on the whole, proved successful in diminishing the incidence of colds when large controlled series have been investigated.

Inoculation with a composite vaccine has been proposed

<sup>19</sup> *Loc cit*

for the purpose of diminishing the frequency and severity of the complications of colds Kneeland<sup>20</sup> compares the results in 23 infants given a course of 9 and later of 7 inoculations, with an equal number of controls. There was no difference in the incidence of minor respiratory infections of the type of the common cold in the two groups. The severity of the subsequent respiratory disease measured by the duration of fever, however, was diminished and there were 2 cases of pneumonia in the vaccinated against 5 in the controls. Further carefully controlled experiments of a similar nature are desirable before a favorable effect can be regarded as established.

Colds are self limited. There is no specific treatment. Symptoms may be relieved and it is possible that complications may be averted by observance of certain precautions. In all cases, while there is fever, rest in bed is desirable. Irrespective of fever, in the more severe types and in infants and the aged or infirm, rest in bed is also advisable. During the disease and also while cough and expectoration persist, caution should be exercised against fatigue, chilling of the body, exposure to draughts without sufficient clothing and rapid cooling when overheated. An abundant intake of fluid is to be recommended and a mild laxative, if necessary, for constipation.

Headache and general discomfort may be alleviated by acetyl-salicylic acid (aspirin), 5 grains, repeated if necessary, every four to six hours for 4 to 6 doses, or such coal tar products as phenacetine, 3 grains, with caffeine, 1 grain, repeated if necessary, every three hours for 3 or 4 doses may be used if these symptoms are sufficiently troublesome. It is undesirable to use amidopyrine or drugs in combination with it, in view of its probable implication as a cause of agranulocytosis in susceptible individuals. If the headache and general pains are especially distressing, Dover's powder, 10 grains, may be ordered. In the investigations of Diehl<sup>21</sup> the highest percentage of good results followed the use of a combination of codeine and papaverine, 1 c, "co-pavin," containing codeine sulphate  $\frac{1}{4}$  grain and papaverine hydrochloride  $\frac{1}{4}$

<sup>20</sup> Jour Exp Med 60 655 1934

<sup>21</sup> New York State Jour Med., 35 109 Feb 1, 1935



grain Toxic symptoms occurred in 4.9 per cent of the cases. In his experience, this preparation as well as certain other opium derivatives were followed by prompt diminution or complete relief of nasal discharge and congestion. The routine use of opium or its derivatives does not seem justifiable, but may be desirable in unusually severe cases. The local application of 1 per cent ephedrine sulphate dropped in the nose produced temporary relief of nasal congestion, but the progress of the cold was apparently unaffected. Toxic symptoms were observed in 4.3 per cent.

## CLINIC OF DR WILLIAM H. ROBEY

### BOSTON CITY HOSPITAL

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#### THE SIGNIFICANCE AND INTERPRETATION OF HEART MURMURS IN GENERAL PRACTICE

If you are surprised that one takes the time to discuss this subject when so much study is being given to the problems of cardiac muscle efficiency, let me remind you that the cardiac murmur is still a puzzle to many general practitioners. In my student days no cardiac sign was given as much thought as the murmur, and its discovery often meant a diagnosis of organic heart disease, even when the patient was apparently in perfect health, since it was impossible for the doctor to believe that a heart could emit such a sound unless diseased. As a result, a diagnosis of cardiac disease was made and the patient's life restricted, with the further result, in some cases, of transforming a healthy person into a hypochondriac. For several years I gave a course to graduate students, principally those who had been undergraduates during the days when the cardiac murmur was considered to be of such great importance. Upon being asked to examine a heart, the student immediately placed a stethoscope over the valve areas and his opinion was formed by the presence or absence of a murmur. Before the end of the course the students were trained to evaluate the medical history and many cardiac and circulatory signs before using the stethoscope. Undergraduates were also taught to diagnose well marked cases of mitral stenosis by palpation of the precordium and the radial pulse before listening to the heart. The idea was to instill in the mind of the student the necessity of merely adding a murmur to the other physical signs rather than allowing the murmur to become the dominant factor in cardiac diagnoses. The physician must constantly remember

that serious heart disease, such as syphilitic aortitis, hypertensive heart disease and coronary disease, may exist without any murmurs. I once saw a forty-seven-year-old man, apparently in the pink of condition, who had no cardiac nor circulatory defect which could be discovered, but who had repeated attacks of most severe nocturnal angina pectoris, one of which terminated in sudden death. Again, some conditions, while slight, may give rise to loud murmurs which disappear with a serious advance of the disease. In hypertensive heart disease a sudden drop in pressure and the disappearance of a mitral systolic murmur are often ominous signs of cardiac muscle failure. In mitral stenosis the presystolic diastolic murmur generally disappears with the onset of auricular fibrillation, although not always.

The mechanical causes of murmurs, such as changes in viscosity of the blood or stretching of the valve rings, have been discussed for years and need not concern us now. The important points to remember are the following:

Murmurs are caused by the vibration of the valve cusps and walls of the heart and of the great vessels when the blood flows from a passage of narrowed caliber to one of much greater caliber, or by the vibration of some tissue attached to a valve, to the heart wall, or to a vessel wall, with the other end free to move in the blood stream. Speed and strength of the blood flow are the factors which intensify or diminish the sound of murmurs. If the flow is strong the murmur will be loud, if of decreased strength the murmur will be faint, while it may disappear completely if the flow loses power to a marked degree. In mitral stenosis, for example, when the left auricle is well compensated and the valve is somewhat distorted, a rough, vibratory presystolic type of diastolic murmur is heard, but when the auricle goes into fibrillation the speed is increased but the strength of flow is reduced so that the murmur subsides or varies in degree of intensity, or it even may cease to exist.

Another cause of murmurs is edema of the cardiac structures which occurs in some of the acute infections, especially rheumatic fever. Such murmurs must be classed during the illness as functional and not as organic until their character and permanence can be determined. Therefore, when mur-

murs are heard during an acute illness, the attending physician should not give a hasty opinion as to their significance

Murmurs, like other heart sounds, may be louder in thin persons and fainter in the obese or muscular. Emphysema may diminish the intensity by pushing the heart away from the chest wall. Fluid accumulating within the pericardial sac, especially when evenly or anteriorly placed, will render less clear all heart sounds

### THE SYSTOLIC MURMUR

As has already been said, the systolic murmur has been the cause of much perplexity in the minds of examiners. During the World War it was, of necessity, given considerable attention, doubtless many healthy young men were declined for service merely because of a sound which suggested a systolic murmur. Some, however, were enlisted and the regimental surgeon sent them to the base hospital with the question of discharge. The consultant's duty was to decide whether the murmur was organic or functional—whether or not it was indicative of some organic lesion which would declare itself under the stress of action. We went into the medical history with great care and looked for further signs. If the findings were otherwise negative we made a diagnosis of functional murmur and signed the soldier for full duty. Similarly Sir Thomas Lewis returned thousands to the front who proved able to carry on successfully. Some have even gone to the point of saying that the mitral systolic murmur is of no importance, and that it may be disregarded in the young unless there are indications of mitral stenosis. Indeed, this might be so, were it not for the fact that the first murmur of mitral stenosis is sometimes the mitral systolic murmur. And the opinion that valvular findings are unimportant would also be true, since the myocardial condition is the one which determines the efficiency of the circulation, were it not that the state of the valves, especially in the young, regulates in a measure, the amount of work which may safely be thrown upon various parts of the heart muscle.

When I read some descriptions of the differentiation between functional and organic systolic murmurs, I am reminded

of one of our professors whom I, as a student, asked when a case of appendicitis should be operated upon. He replied, "Show me the case." Laennec in 1819 described sounds in the heart which he considered were always caused by valvular lesions, but later he denied them any value because the post-mortem examination often failed to show the lesion which had been foretold by the murmur. This failure to discriminate between functional and organic murmurs continued for years, notwithstanding our great advance in the interpretation of cardiac and circulatory signs, even today some confusion on this point continues to exist.

The two chief findings in the determination of a systolic murmur are duration and intensity, and of these, the former is the more important. To make a definite diagnosis of a systolic murmur the bruit must have an appreciable duration after the first sound, and continue into systole. Do not mistake a slight prolongation of the first sound for a murmur.

Short, faint systolic murmurs are considered functional and of little importance, while prolonged intense ones are thought to be organic. Levine<sup>1</sup> grades mitral systolic murmurs by their intensity, which he divides into six degrees, beginning with the first, which is very faint and which he says few general practitioners hear, and ending with the sixth, which is rare, but so intense that it can sometimes be heard when merely standing in front of the patient (in my own experience I remember but one such extreme case) and physicians working with him in the clinic were able in most instances to estimate the degree of intensity of a murmur and were usually in entire agreement. This is a very interesting method for a group under expert leadership, but for those who must work alone and whose training may not have been specialized, it offers comparatively little that is of practical advantage.

Intensity is important, but differing conditions in patients suffering from the same lesion may cause it to vary—this refers to emphysema, thick chest wall, and the degree of cardiac muscle strength. Duration can be more easily determined following the rules already given.

While systolic murmurs are said to occur rarely in normal individuals, many are heard without other evidence of cardiac

<sup>1</sup> Jour Amer Med Assoc, 101 436-438, Aug 5, 1933

disease When one is heard we immediately attempt to decide whether it represents organic valvular disease or is merely a functional murmur Regurgitation of blood through the mitral valve produces a systolic murmur over the area of cardiac impulse, but regurgitation of blood and its systolic murmur do not necessarily indicate disease of the mitral valve When the New England Heart Association in 1926 made a survey of the 119,337 school children of Boston, 2311 who, because of murmurs, were suspected by the school physicians of some type of heart disease, were examined and separated into groups The majority, 1344, could be safely reassured they had no significant disease The doubtful group, 265, required reexamination until the diagnosis could be settled The potential heart disease group needed to have the importance of their condition brought home to them The most important discovery was the small number of children having organic disease—only 160 were in hospitals, and these, added to the ambulatory cases, totaled 785, or the surprisingly low percentage of 0.66 of discovered cases In one room where there were 52 young children, every one had what the school physicians called a systolic murmur, and yet the medical history, physical well being, activity and absence of other cardiac abnormalities made us pass the hearts as normal

Conditions which dilate the left ventricle may enlarge the valve opening so that perfectly normal valve cusps may not be able to approximate and will therefore fail to prevent a reflux of blood from ventricle to auricle during the contraction of the former chamber On the other hand, the chambers of the heart and the mitral ring may be normal, yet the cusps are retracted, the valve is incompetent and a murmur occurs during ventricular systole

A mitral systolic murmur in a young person, especially if it has the proper duration and some degree of intensity, should be looked upon as evidence of organic valvular disease until we can satisfy ourselves that it is functional, while a similar murmur in an elderly person is very apt to be functional and not caused by any pathological changes in the valve itself, but is a result of cardiac muscle pathology In fact, many serious cardiac disturbances in the elderly occur without any murmur In the young it is far more important,

meaning, as it does, when we have proved it to be organic, a pathological condition of the valve which gradually throws more work upon adjacent chambers and eventually causes an inefficient heart

How are we to determine whether a mitral systolic murmur is functional or organic? First of all, there is the medical history. Has the patient ever had rheumatic fever or its allies? We must remember that rheumatic fever in a child frequently has quite a different train of symptoms from that in an adult, he may have a sore throat, vague pains in the muscles, fever, nervousness and irritability, or there may be repeated attacks of sore throat without other symptoms which the patient or his family are able to recall, but the hot, red, painful joints of the adult are often not in evidence. The diagnosis of rheumatic heart disease is almost certain, even if the other signs of mitral stenosis cannot be demonstrated, provided one finds that the murmur has duration and a certain degree of intensity combined with a history of rheumatic fever

A seventeen-year-old girl was brought to my office with a history of always being delicate. During the summer she had lost 12 pounds, although she was on a farm. She gave a history of rather frequent colds but no rheumatic fever, sore throats nor tonsillitis. Occasionally there was nose-bleed. She had a good appetite and slept well, her chief complaint was very easy fatigue. If she went out for an evening she would be tired the following day. She was thin and of poor color. The blood pressure was 130-90. The heart was normal to percussion and fluoroscope with a loud, blowing systolic murmur heard over the entire precordia and in the back. The impulse was heaving and the cardiac rate 120. There was no arrhythmia, no diastolic nor presystolic murmur, no thyroid enlargement, no cardiac thrill, no tremor of hands, no incoordination. The lungs and abdomen were negative. There was no edema. The hands were cold and slightly cyanotic. In the differential diagnosis, I considered first mitral stenosis and then effort syndrome and hyperthyroidism. In view of the fatigue, occasional nosebleeds and marked systolic murmur, the mitral stenosis seemed most probable. She was given a régime of rest and quiet with instructions to report in two weeks, but six days after I saw her, her mother stated that her daughter had a paralysis of the left arm and leg. This clarified the diagnosis of mitral stenosis. Two months later I saw her in consultation with her physician and found, in addition to the hemiplegia, a systolic murmur, diastolic and presystolic murmurs and a marked apical thrill. The pulse was small and 140 in rate.

Another girl entered the hospital many years ago with a systolic apical murmur of moderate intensity without any murmurs during diastole. There was no history of rheumatic fever but there had been occasional attacks of nosebleed. She was discharged with a diagnosis of mitral regurgitation but

returned in about two weeks with a diastolic murmur in addition to her systolic one and a certain amount of arrhythmia. This made the diagnosis of mitral stenosis quite apparent

If we can satisfy ourselves that there is some cardiac enlargement with a persistent mitral systolic murmur it can be assumed that there is organic valvular disease. Similar findings in a middle-aged person who is developing easy fatigue, breathlessness on exertion or during sleep, or some type of arrhythmia doubtless would indicate organic cardiac disease but the murmur is merely relative. During the course of rheumatic fever, the physician should reserve his opinion about any murmurs he may hear until the fever has entirely subsided and the patient's convalescence has been well established.

A fourteen year-old girl was on our service at the Boston City Hospital with a violent and prolonged attack of rheumatic fever and during the height of the disease she developed a well marked presystolic murmur. There was a temptation to make a diagnosis of mitral stenosis but it seemed incredible that such a condition could have developed in so short a time, and the diagnosis was held in abeyance. As convalescence progressed nothing was heard in the heart but a soft blowing systolic murmur. Doubtless this girl eventually had the signs of organic mitral stenosis but at the time we heard the presystolic murmur she probably had a functional stenosis due to edema about the valve ring and when the inflammation subsided the edema disappeared and with it the murmur.

Winternitz and his associates have demonstrated the reason for the appearance and disappearance of these murmurs, but Sir James Mackenzie in reporting two such cases gives no explanation.

Basal systolic murmurs are principally heard at the so-called aortic and pulmonic areas. Not infrequently a soft, blowing systolic murmur is heard over the aortic area in the middle aged and elderly, particularly among males, and is an indication of sclerotic changes in the aortic ring. The murmur is often transmitted to the pulmonic area and with diminishing intensity to the mitral region. It may have for a long time no accompanying signs, but more frequently there is some widening of the great vessels, a sharp closing of the aortic valve, an increase in the measurements of the heart, and some heightening of the blood pressure, particularly the diastolic. I have known physicians to interpret the aortic systolic mur-



mur as a sign of aortic stenosis but the murmur of that lesion is quite different. The latter is definitely limited in area, often no larger than the bell of a Bowles stethoscope, is rough and grating in quality, as stenotic murmurs are apt to be, is accompanied by a palpable thrill, absence of the second sound, and transmission to the vessels of the neck. The murmur of early stenosis may be very slight but with increasing obstruction to the blood stream it may become extremely loud, and when transmitted to the entire chest it may on occasion be heard a short distance from the wall with the unaided ear, in addition, there is the plateau or sustained pulse. With stenosis there is also regurgitation in most cases, and therefore a diastolic murmur.

The systolic murmur at the pulmonic area is frequently heard and is the commonest of all murmurs. It may be audible when the patient is lying down and not at all in the upright position. Unless it is heard with considerable intensity in both positions it may be classed as functional or physiological. The murmur is often of a soft, blowing quality, which begins early in systole and extends through most of it, but does not obscure the first sound, the pulmonic second sound is frequently accentuated.

The organic systolic murmurs in the pulmonic area are much rarer. The harsh murmurs of congenital pulmonic stenosis and acquired pulmonic stenosis have a very limited area and are usually accompanied by a rough thrill. The former condition is accompanied by cyanosis, a frail physique, easy fatigue and early cardiac failure, while the latter may be compatible with reasonably good health and a sense of well-being for many years. In the cases I have seen, the difference between the general condition of the patients with congenital lesions and that of those with acquired lesions is very striking. The nearness of the so-called "valve areas" and the similarity of the murmurs in aortic stenosis and pulmonary stenosis make the differential diagnosis sometimes quite difficult or even impossible. Other physical findings and history must be used to their fullest extent in such cases.

Cardiorespiratory murmurs are most commonly heard along the left border of the heart. They are usually systolic in time, very rarely diastolic. They are due to the pressure of

the heart against the lung during systole or to the squeezing of air from the lung during the contraction, or to old adhesions between the pleura and pericardium. Sometimes a history of pneumonia or a healed tuberculosis may explain it. Other physical signs will of course be absent and if it can be determined that the murmur is respiratory it has no importance. In like manner obesity, upward pressure of the diaphragm or tumors of the chest may be the cause of systolic murmurs. Over the base of the heart, aneurysm, dilatation, constriction from without, or any deformity, may cause murmurs in the great vessels as well as in the peripheral

### THE DIASTOLIC MURMURS

The diastolic murmur is more difficult to hear than the systolic murmur and of much greater importance. It is occasionally functional without valve involvement when changes occur in the aorta in hypertension and arteriosclerosis. It is practically never an unimportant murmur, as is the systolic in numerous instances. It occurs in two organic conditions, aortic regurgitation and mitral stenosis.

In aortic regurgitation the murmur is soft and blowing, it may be heard over the aortic area or over the entire precordium, but it is usually of greatest intensity along the left border of the sternum at about the third and fourth interspaces. Because it occupies all of diastole it usually entirely obscures the second sound. In well marked cases of aortic regurgitation there is lateral and downward enlargement of the heart with the cardiac impulse in the sixth interspace, throbbing of the carotids with head nodding, pulsation of the retinal vessels, the characteristic Corrigan or "waterhammer" pulse, often a normal or high systolic blood pressure with a very low or almost absent diastolic pressure, giving the typical high pulse pressure of the lesion, throbbing of the femoral, iliac, posterior tibial and dorsalis pedis vessels with the typical sharp systolic shock known as the "pistol shot," heard with the stethoscope over these vessels, especially the femoral and iliacs, not infrequently over the iliacs systolic and diastolic murmurs are heard—known as Duroziez's sign. In more marked cases, especially with a high pulse pressure, there is a capillary pulse but a little care must be used in its detection.

this sign, as it may occur in some who have not aortic regurgitation, or even in normal individuals. The best method is to rub the forehead with a tongue depressor until it is hyperemic and as the redness begins to disappear the pulse may be seen as a rhythmically recurring blush. Do not stand too near the patient if you wish to see it to the best advantage.

Sometimes patients have entered the hospital with many of the physical signs of aortic regurgitation but the murmur does not appear until there has been a rest in bed for several days, when, with increased muscle tone, it appears with its usual qualities.

The earliest murmur of mitral stenosis is mid-diastolic, soft, blowing and often difficult to hear. In every case with an apical systolic murmur, especially if of sufficient duration, intensity and persistence, the mid-diastolic murmur should be carefully sought. All murmurs vary with the amount of muscle force in the heart, with the cardiac rate and with the rhythm. So the early soft murmur may be mid-diastolic where the rate is normal and the rhythm fairly regular, sometimes it may be late diastolic or it may be early diastolic, especially when it precedes and merges into the rough diastolic, ending in a sharp first sound, the murmur often spoken of as presystolic. Years ago the presystolic was considered the determining diagnostic sign of mitral stenosis—often the disease was not recognized until this rough, sometimes called crescendo, murmur was heard. It is accompanied by a thrill, a heaving cardiac impulse and by a radial pulse small in volume and of low tension. The thrill is also presystolic but too much effort need not be expended in determining its exact time—if it is fairly marked and accompanies a presystolic murmur, that is enough. It is agreed that the murmurs of mitral stenosis are caused by left-auricular systole and therefore they are soft diastolic at first, but as the warping and stenosis of the valve advance while the muscle force of the auricle remains fairly normal, the blood in passing through the narrowed opening causes a rough murmur and a palpable vibration. This roughness often disappears with dilatation of the auricle and with the onset of marked arrhythmia, in auricular fibrillation especially, the murmurs may be entirely absent or heard only in the longer diastolic spaces. When a blowing diastolic

murmur is audible at the area of cardiac impulse there should be little doubt about its significance—it is probably organic. Aortic regurgitation occurs at a valve opening which is concerned with the second sound of the heart and the regurgitant blood stream obscures the sound of its closure. The diastolic murmur of mitral stenosis occurs at a valve unrelated to the second sound, therefore is unobstructive to it. The shape of the heart, the position of the cardiac impulse, the character of the pulse, the sounds in the blood vessels are all quite different in the two conditions.

Sometimes young persons with thin chests, who are nervous about being examined, especially by a new physician, may present what appears to be a vibratory murmur accompanied by a thrill which later entirely disappears. Another condition producing a relative mitral stenosis without actual damage to the mitral valve is probably left ventricular dilatation.

Two conditions seem to produce a relative mitral stenosis, more commonly aortic regurgitation and less frequently dilatation associated with adherent pericardium. Several theories have been advanced over the years to account for relative mitral stenosis. The time relations and other characteristics of the murmur are the same as in organic mitral stenosis, except that the murmur is usually less intense and is unaccompanied by a thrill. When the mitral diastolic murmur just described accompanies aortic regurgitation it is known as the Austin Flint murmur. In cases of organic mitral stenosis associated with aortic regurgitation, the lessened volume of blood caused by the stenosis often has a modifying effect upon the Corrigan pulse but this is not the case with a merely functional mitral diastolic murmur.

Pulmonary regurgitation is very rare but its murmur has all the characteristics of the diastolic murmur of aortic regurgitation. While the latter is best heard along the left border of the sternum, the murmur of pulmonary regurgitation is equally loud or may be louder in the pulmonic area, but it is unaccompanied by signs in the peripheral circulation so characteristic of aortic regurgitation. Radiographic studies of the lungs for pulsations and abnormal right-axis deviation in the electrocardiogram will help to differentiate the pulmonary regurgitation murmur from the aortic. Mitral

stenosis, by causing increased pulmonary tension, and therefore dilatation of the pulmonary artery and valve ring without valve pathology, may cause pulmonary regurgitation and the diastolic murmur thus produced is known as the Graham Steell murmur

Other causes which must be considered are acute or chronic endocarditis of the valve as illustrated by a case seen a few years ago with a gonococcus involvement of the pulmonary valve, chronic disease of the lungs, sometimes extended patency of the ductus arteriosus and congenital defects which give rise to regurgitation as a sequel of stenosis

#### PERICARDIAL FRICTION RUBS

We have heard physicians debating the differentiation between double murmurs and the pericardial friction rub. The rub may be mistaken for murmurs, especially if the sound is soft, faint, and audible only in systole, where it is often heard much better, because contraction is more active than filling. If you listen very carefully during diastole you will hear an exactly similar sound, although at times much fainter. The unmistakable pericardial friction rub is rough and rasping during systole and of similar quality during diastole, and may be accompanied by a palpable thrill. Another important point is that pericardial rubs often change their position in the precordial area from day to day, as organic murmurs never do. When the friction rub is present it may obscure valve murmurs. Let me illustrate what I mean by the change in position of the pericardial rub, by recalling an incident reported some years ago. The quest for a case of aortic stenosis in the hospital resulted in my being shown a twenty-seven-year-old male patient convalescent from acute rheumatism and having the condition I was in search of, according to the diagnosis. The man looked well and said that all of his symptoms had subsided. On listening over the aortic area, a rough, grating, systolic murmur was heard and also a very faint murmur of similar quality in diastole. There were no cardiac nor circulatory signs indicating aortic stenosis or regurgitation. In the absence of confirmatory signs of valvular disease and taking into account his recent attack of acute rheumatism, a pericardial friction rub seemed probable. Two days later the

rough systolic sound and the fainter diastolic were heard over the third interspace to the left of the sternum, the following day over the fourth and by the fifth day they were barely audible just above the cardiac impulse and then disappeared—in other words there was no aortic stenosis, but there was a pericardial friction rub. During acute infections, especially rheumatic fever, the precordium should be explored for friction sounds, knowing that they may be very transitory, but once heard, if only for a brief period, we should make a keener search for valve murmurs, since we know that myocardium, endocardium and pericardium are probably all involved, although in varying degrees.

#### TO-AND-FRO OR CONTINUOUS MURMURS

The commonest and least important of the continuous murmurs, one long known to physicians, is the venous hum in the neck. It is loudest at the base of the right side, less loud on the left, is heard in many normal individuals, especially children, and is important to consider only because it may be transmitted to the base of the heart, where it may give rise to an erroneous diagnosis of aortic regurgitation, especially if the diastolic part of the hum happens to be prominent. The absence of other signs of valvular lesions will dispel their diagnoses.

Patency of the ductus arteriosus gives a see-saw murmur louder in systole and best heard in the first or second interspace to the left of the sternum. Probably no other murmur has this continuous, grinding character throughout the cardiac cycle, and if it can be distinguished from the venous hum in the neck and arteriovenous aneurysms it is usually pathognomonic.

#### SUMMARY

Murmurs are merely a part, sometimes a very small part, of the complete cardiac and circulatory examination.

Medical history should be thorough and searching, as an aid in estimating the importance of any murmur.

During the course of acute infections, especially rheumatic fever, there should be no haste on the part of the medical attendant to reach a conclusion concerning a murmur. Convalescence may entirely change the cardiac findings.

If a murmur is heard during a routine physical examination, some information about it should be given to the patient or his relatives, because if it is passed without comment another physician at a subsequent examination may unduly alarm the patient and you will be considered remiss

The systolic murmur is much commoner than the diastolic, easier to hear but often more difficult to interpret. The systolic murmur is more often functional than any other. The duration and intensity of a systolic murmur should be carefully studied. If the evidence points to a functional murmur the patient should be seen at regular intervals to substantiate the opinion, because it is well known that many systolic murmurs which are classed as benign because there is no other evidence of cardiac inefficiency, are actually the earliest indication of serious valvular pathology. The louder systolic murmurs are usually associated with organic cardiac disease.

If the physician keeps the normal physiology of the valves in mind he will not have to burden his memory with the time and character of murmurs produced by valve pathology.

Simple murmurs do not require treatment, while organic ones demand whatever the cardiac inefficiency requires.

## CLINIC OF DR EDWARD S EMERY, JR

PETER BENT BRIGHAM HOSPITAL

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### THE DIAGNOSIS AND MANAGEMENT OF THE CHRONIC OBSTRUCTIVE TYPE OF PEPTIC ULCER

To treat successfully a patient with a peptic ulcer and chronic obstruction, one should know when an obstruction is in fact chronic and when surgery is indicated for its alleviation.

Ulcers may produce all grades of obstruction. There is the transient obstruction, which is obviously the result of a pylorospasm. Then there is the permanent type, which shows little fluctuation but may progress over a series of years. This kind of obstruction can be divided arbitrarily into two categories, the one which subsides on a good medical régime and the one that does not. A word should be said at this place about the cause of the more permanent types of obstruction. It has been taught for years that the obstruction which responds to medical treatment is the result of spasm and edema and that the other group is produced by a cicatrization of the pylorus. This teaching seems to have been based on pure reason without observation, for there is really very little, if anything, to substantiate the idea of a true cicatrization. In a recent conversation with a pathologist of wide experience, he stated that he had never seen a cicatrized pylorus due to ulcer. The late B. W. Sippy used to teach that retention disappeared on his treatment at the end of three months in 50 per cent of the cases and at the end of nine months in 85 per cent. Therefore, it is reasonable to believe that obstruction results from spasm and hypertrophy of the pylorus in most, if not all, of the cases. This complication should ultimately respond to medical treatment in virtually all cases, if



the treatment is persisted in thoroughly enough and long enough. Hence the former principle of treatment, that obstruction requires surgery because of the nature of the condition, does not seem to be correct. Surgery should be resorted to when it will relieve retention more easily than medical treatment, and thus save the patient time and spare him an adherence to a very strict and long continued régime.

The decision of when to use surgery may be decided on one or more of the following aids to diagnosis: (1) The roentgenographic findings. (2) Evidence from gastric aspirations of undue retention. (3) A history of obstructive symptoms. (4) The failure or otherwise for the obstruction to respond to medical treatment. In evaluating the use of the x-ray in the diagnosis of obstruction, one must remember that this method of investigation merely reveals visual evidence of what seems to be taking place in the stomach. The roentgenologist deduces from the available evidence whether or not an obstruction is present. One of his aids to diagnosis is the presence of retention, the amount of which is usually expressed in percentage of the total amount of barium ingested. Retention alone is not evidence for obstruction because complete retention may result from a lack of peristalsis. This situation occurs most frequently under the influence of a headache or emotion, frequently precipitated by worry over having the roentgenographic study.

The type of peristalsis is a further aid to the roentgenologist. Increased resistance to the outflow of the gastric contents produces more work for the stomach with a resulting hypertrophy of that organ. Therefore, marked grades of stenosis are accompanied by deep peristaltic waves. The presence of a large retention associated with increased peristalsis usually is good evidence for a so-called "high-grade" obstruction. However, since all degrees of hypertrophy may be encountered, and since hyperperistalsis in the absence of anything more than pylorospasm can occur, it is not always easy to differentiate between the two. In such situations a history of obstructive symptoms is useful evidence although not infallible. Some patients vomit more readily than others. It is not uncommon to find individuals with almost complete stenosis, who have never vomited, in contradistinction to others



suitable treatment for these patients, because clinical studies demonstrate that sole reliance on the x-ray does not give the best criteria for treatment. At the Peter Bent Brigham Hospital medical treatment was effective in only 38.6 per cent of the cases in which the gastric aspirations and the history agreed with the roentgen findings, whereas, it was of benefit in 68.2 per cent of the cases in which the roentgenogram alone suggested retention. The retention in many of the latter group was doubtless the result of temporary spasm. It is evident from this data that reliance on roentgen evidence alone will result in subjecting an unnecessarily large number of patients to surgery.

This difficulty can be offset by utilizing the final method of study that was mentioned, namely, putting the patient on a good medical régime. This medical treatment should be effective in overcoming the known causes of irritation, namely, the hydrochloric acid and the effect of prolonged gastric residues. This is accomplished most satisfactorily by a Sippy régime with gastric lavage every night and again in the morning, if there is found to be an increase in the fasting contents. This treatment should be continued if a large retention subsides quickly. The persistence of a large retention after a week to ten days usually means a marked obstruction and surgery might as well be used at once. Meanwhile, no time has been wasted because these patients do better if they are prepared with frequent gastric lavages.

Medical treatment should be continued for six weeks to three months on patients with moderate retention. Six weeks is a minimum period on which to gauge the effect of treatment, because it seems to require this length of time for moderate degrees of pylorospasm to subside. In fact, the first effect of medical treatment may be an increase in retention which later subsides. This phenomenon is caused in all probability by a decrease in excessive peristalsis before a decrease in obstruction takes place.

Three months usually is long enough to decide whether the obstruction is responding in a satisfactory way to medical treatment. Although most cases should respond ultimately, if one persists in treatment long enough, usually it is better to use surgery after three months, if very definite improvement

has not occurred. Some guide as to what constitutes a satisfactory response is given by the results obtained in this clinic. It has been found that the end-results of treating a gastric retention under 40 per cent is similar with medical or surgical therapy. Because this figure was obtained before patients had had any treatment, it is wiser to use a lower figure after medical treatment has been used. Hence, it is good practice to operate upon a patient who still has a 30 per cent retention by the x ray after three months of good medical treatment.

This gives us a plan for treating ulcer patients with retention. One should employ surgery for patients with a gastric retention of 40 per cent or over, who have evidence of a long-standing pyloric obstruction, as shown by deep peristaltic waves due to hypertrophy.

Patients with a retention of 40 per cent or over but without evidence of hypertrophy by the x ray should have a preliminary trial with medical treatment.

For the patient with a large original retention of 60 per cent or over, which may be due to either temporary inhibition of peristalsis or to obstruction, a period of seven to ten days on medical treatment usually is sufficient to decide which kind of treatment to use.

For all other patients with a retention of 40 per cent, medical or surgical treatment give equally good results.

The following illustrative case demonstrates what can be accomplished by careful medical treatment.

J. J. O., a fifty-eight year-old rent collector had had symptoms of ulcer for twenty years, when first seen in 1929. At the time he consulted us he was troubled chiefly by the rumbling of gas and fullness. He had not vomited. Physical examination was essentially negative. A roentgen examination reported a 90 per cent retention with an obstructive type of peristalsis. He was referred to the hospital wards and placed on a Sippy régime with aspirations each night. After four weeks of this treatment, the stomach was hypertonic, showed vigorous peristalsis, but the residue had decreased to 5 per cent. One month after discharge from the hospital the stomach still showed vigorous peristalsis and a 10 per cent residue. At this time he was given the choice of surgery or of continuing with daily aspirations but he preferred to go on as before. He remained on a Sippy régime with daily aspirations for another year. He was then obtaining 750 to 900 cc. of gastric contents each night. Because the ulcer had given no symptoms for a year the Sippy treatment was stopped, and the patient was put on a carefully supervised list of foods with five feedings a day. He continued this dietary treatment with aspirations every night for the next two years. For the last two years he has aspirated

only occasionally The retention has steadily diminished until now he aspirates only 200 cc three hours after supper, and there was no retention by x-ray at the last examination

Most patients would prefer surgery to undergoing such a long and vigorous medical treatment, but the case illustrates that marked obstruction will respond to medical treatment and it is, therefore, always justifiable to determine the effect of medical treatment on obstruction due to ulcer before instituting surgery

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### THE CLINICAL IMPORTANCE OF THE SEQUENCE OF EVENTS IN BONE MARROW FAILURE

ABNORMALITIES in the peripheral blood picture must be interpreted with caution and with due regard for certain physiological principles and clinical facts. In both hospital and private practice we not infrequently encounter patients with unusual blood findings which reflect but poorly the true underlying pathological condition, which may indeed be due to abnormalities in systems other than the hematopoietic. Blood pictures varying but little from the normal may be associated with the early stages of the most fatal blood diseases and, on the other hand, marked changes may be but temporary and not due to any fundamental or serious bone marrow dyscrasia.

The following cases illustrate certain points in diagnosis and prognosis which may be of interest to the clinician.

**Case I.**—A married woman\* of thirty five years had been taking 1½ grains of dinitrophenol intermittently for the past year. During the two weeks prior to admission to the hospital she had taken approximately 21 grains of the drug and had lost 7 pounds in weight. Six days prior to admission she had an attack of acute tonsillitis, for which she was treated symptomatically. On the sixth day of this illness she appeared definitely worse and was taken to the hospital on May 14 1935. Then for the first time her blood was studied. The white blood cell count was 900 per cubic millimeter the red blood cell count 3,320,000, the hemoglobin 62 per cent. Examination of the blood smear

\*I am indebted to Dr Stanley Imberman of Los Angeles for permission to cite this case

showed 94 per cent lymphocytes and 6 per cent eosinophils. The platelets were slightly decreased. Her temperature was 104° F, the pulse 130, the respirations 20. Both tonsils were enlarged, ulcerated, and covered with a grayish membrane. The soft palate, uvula and pharynx were acutely inflamed. Cultures for the throat were negative for diphtheria bacilli. The urine contained a trace of albumen, an occasional cast, and a few red blood cells. A diagnosis of agranulocytosis secondary to dinitrophenol therapy was made and the patient immediately started on pentnucleotide, 10 cc intramuscularly four times a day. This she bore without untoward reactions. In addition 3 cc of liver extract were given each day. Appropriate symptomatic treatment was, of course, continued and all dinitrophenol medication stopped.

From a clinical point of view she remained very ill, semiconscious and irrational, but on May 18, four days after admission, the white blood cell count had risen to 1700 per cubic centimeter, and there were found in the smear 19.2 per cent polymorphonuclear neutrophils, 16.2 per cent monocytes, 61.2 per cent lymphocytes, 1.5 per cent eosinophils, and 1.9 per cent unclassified cells. The throat condition seemed definitely improved. The pentnucleotide was continued in full doses.

Three days later, on May 21, the patient's clinical condition was greatly improved and the temperature dropped to normal. The white blood cell count had risen to 4000 per cubic millimeter and the neutrophils were 35 per cent, but coincidentally the platelets had fallen to 30,000 per cubic millimeter. The red blood cell count was still 3,300,000 per cubic millimeter. Many petechiae were noted scattered over the body and in the mucous membranes. The platelet decrease, however, proved to be of an evanescent nature, for five days later the blood contained a normal number of these elements and there was no further hemorrhagic tendency. Moreover, the white blood cell count had then risen to 12,000 per cubic millimeter, and the polymorphonuclear neutrophils to 65 per cent. Pentnucleotide was then discontinued.

But by this time, two weeks after entry, the red blood cell count had fallen to 2,900,000 per cubic millimeter, and the hemoglobin to 56 per cent. A week later the red blood cell count had fallen still further to 2,500,000 per cubic millimeter. This slowly developing anemia, together with at least temporary marked reduction of platelets with attendant hemorrhages, aroused the suspicion that the condition was in reality a true aplastic anemia or pancytopenia and the fear was expressed by some that a fatal termination might be looked forward to. Such, however, was not my opinion. It may correctly be assumed in this instance that the dinitrophenol was the cause of the existing blood dyscrasia. It may further be assumed that on or about May 5 the toxic action of this substance had reached a sufficient degree to destroy or suppress, in large parts at least, the existing active bone marrow. The first outward and visible effect of such an action would be the partial or complete disappearance of the polymorphonuclear neutrophils, whose natural life in the peripheral blood is probably a matter of a few hours or at most a few days. This finding, together with the recognition of its significance, resulted in the withdrawal of the causative agent and the initiation of those measures which at present seem most likely to result in a stimulation of the granulocytic elements of the bone marrow. It is a matter of record that these cells did reappear in considerable numbers in less than a week. There was, therefore, tangible and unequivocal evidence that the bone marrow was recovering, at least in so far as the granular series was concerned.

With the red cell series the situation is quite different. The average life of a red cell in the peripheral blood is generally conceded to be from three to six weeks. The rate of formation of new red blood cells proceeds slowly, never with the dramatic suddenness with which white cells may be replaced. Under these circumstances it must be obvious that if a bone marrow is virtually wiped out by some toxic agent on a given date, anemia of moment will not make its appearance in the peripheral blood for several weeks. If, in the meantime, the noxious agent has been removed, if such measures as may be regarded as favoring bone marrow recovery have been instituted, and if there become manifest certain signs of recovery of the bone marrow, such as an increase in the white blood cell count, then it may safely be assumed that the anemia, such as developed in this case, is the natural and inevitable result of the original insult and need not necessarily be regarded as indicating the development of a further or more serious disease. Transfusions of blood under these circumstances are not, in my opinion, indicated unless the patient be in actual danger from the anemia *per se*. They may do more harm than good and severe reactions are not uncommon.

In late May two and a half weeks after entry, the white blood cell count had risen to 13,000 per cubic millimeter and the neutrophils to 65 per cent. The temperature, which had been normal for many days again rose. The patient developed a dry hacking cough and complained of pain in the left upper chest. x Ray films showed what appeared to be pneumonia in the left upper lobe. As time passed it became increasingly evident that the process was indeed a pulmonary abscess. For this complication general supportive and symptomatic treatment was instituted. In a month the abscess under this conservative régime was but half its original size. In another month it had entirely disappeared. In the meantime, the red blood cell count rose to a normal figure and by July 13 eight weeks after entry, all abnormalities of the blood had disappeared and the patient was clinically well.

The lesson that such a case teaches is that the development of the various signs of bone marrow insufficiency become manifest at varying intervals after the original provocative injury, leukopenia in a few days, thrombocytopenia probably in a week or so, anemia not for several weeks. The natural history of recovering (or failing) bone marrow must be carefully considered in any diagnosis or prognosis.

The implications derived from such considerations are



broad The late development of anemia following the action of a toxic substance on the bone marrow does not necessarily imply that some new and unexplained insult has resulted In a similar manner the absence of anemia during the early stages of a blood disease does not necessarily rule out those conditions commonly thought of as being associated with profound and progressive anemia This latter point is illustrated by the following case

Case II—On April 22, 1935 I saw with Dr H T French and Dr C C Stewart of Hanover, N H, a boy fourteen years old He had always been strong and well and led a normal and active outdoor life The only fact of any possible moment in his past history was that in infancy his diet had, for a short while, been definitely inadequate and unbalanced For several weeks prior to admission to the hospital he had seemed somewhat lazy and somnolent, he lacked initiative and was inattentive On April 15 he had a severe headache and complained of anorexia, nausea, and occasional vomiting There was no abdominal pain On admission his temperature was 103° F This gradually fell to normal in three days, only to rise again to 102° F on the fourth day On examination at this time (April 22) he was found to be a well-built, strong-looking boy, a little drowsy and listless, but rational and cooperative There was a definite but minimal bilateral horizontal nystagmus The remainder of the physical examination was essentially normal There was no lymph node enlargement in any region The spleen could not be felt even on deep inspiration There was no tenderness, spasm, or masses in the abdomen Neurological examination was normal except for a questionable stiffness of the neck Neither lumbar puncture nor x-ray films of the chest revealed any abnormalities

The red blood cell count was 4,800,000 per cubic millimeter, the hemoglobin 90 per cent, the white blood cell count 2500 per cubic millimeter with 90 per cent normal lymphocytes, 8 per cent polymorphonuclear neutrophils and 2 per cent monocytes The neutrophils showed no evidence of toxic degeneration such as are so frequently seen in the presence of an infection The platelets were normal in number and appearance

The condition was, therefore, essentially one of unexplained leukopenia, neutropenia, and fever Idiopathic agranulocytosis seemed out of the question It is extremely rare at this age Fever of moment in this disease is due to infection secondary to the leukopenia and this infection is almost always obvious on careful examination No such infection was in evidence Furthermore, no drugs had been taken which might logically have been regarded as productive of the leukopenia Leukemia is usually accompanied by progressive anemia, bleeding and the finding of abnormally young cells in the peripheral blood, these features are almost constant once fever has set in Yet it must be recognized that in leukemia of children there may rarely be but moderate departure from the normal white blood cell picture and, as pointed out above, anemia of any great degree does not develop under such conditions until after the lapse of several weeks A diagnosis of leukemia in this case, therefore, could not be summarily discarded It seemed, however, extremely unlikely and was not at any time seriously entertained There remained the possibility of some obscure infection of uncertain nature and unknown locus Such

a diagnosis would not advance our practical knowledge of the case in any way as long, that is as its locus remained unknown

The boy continued to run an irregular fever for three weeks. During this time the white blood cell count ranged from 1500 to 3000 per cubic millimeter and the neutrophils from 10 to 28 per cent. At no time were abnormal or immature white blood cells seen in the smear. Gradually his general condition improved. The fever abated. The blood picture became normal and he returned home apparently well on May 10, approximately four weeks after admission to the hospital.

He remained well until May 25 when once more his temperature rose, this time to 104° F. The initial symptoms of drowsiness reappeared and once more nausea, anorexia and vomiting occurred. Coincidentally the white blood cell count fell to 900 per cubic millimeter and the differential count revealed 100 per cent lymphocytes, all of them normal. The red blood cell count had fallen to 2,500,000 per cubic millimeter and the hemoglobin to 50 per cent. A new element, anemia of unexplained origin had appeared. The physical examination was still essentially normal. There was no enlargement of the lymph nodes or spleen. Examination of the abdomen was negative. The elevated temperature continued and on June 3 reached 105° F. At this time there was definite soreness of the throat and the gums were found to be swollen and spongy. Retinal hemorrhages appeared in both eyes. A third element, the hemorrhagic diathesis, had appeared. The red blood cell count had fallen to 1,600,000 per cubic millimeter.

Now, the significance of the anemia here would appear to be quite different from that in the first case. In that instance there was a definite and removable etiological agent which produced a sequence of events from which anemia was to be expected to develop even in the face of evidence of recovery on the part of the other blood elements. In the case of the boy we were dealing with a leukopenia of unknown origin and fluctuating course to which the subsequent development of anemia added further evidence of a serious bone marrow disease. It seemed evident once anemia and thrombocytopenia had developed that unless some definite and logical cause for the hematological abnormalities could be found one would have to assume a primary and probably irremediable bone marrow disorder.

Nevertheless, the temperature once more gradually came down to normal and there was definite clinical improvement. The white blood cell count rose to 2000 per cubic millimeter and the neutrophils to 24 per cent. The anemia, however, persisted in spite of intensive treatment with iron and liver extract. After this period of improvement the temperature again rose precipitantly, and the red blood cell count fell to 750,000 per cubic millimeter. Not the slightest evidence of regeneration of the red cell series could be found. The white blood cell count dropped to 500 per cubic millimeter, all granular cells disappeared and the boy died in early July, three months after the initial symptoms.

We are indebted to Dr. R. E. Miller of Hanover, N. H. for a study of the necropsy material. The positive findings were few. There was a chronic appendicitis with loss of the mucosa and masses of bacilli, some in phagocytes, in the superficial tissue. In addition there was a slight periportal fibrosis of the liver probably secondary to the appendiceal infection. From the appendix a bacterium of uncertain nature was recovered. The bone marrow was throughout aplastic and cell poor. There was no evidence of leukemic infiltration. On microscopical examination there was obvious a

marked hypoplasia of all the formed elements. Such few cells of the granular series as were present appeared normal. Erythropoiesis was scanty. There was no evidence of invasion by any malignant tumor.

While the case cannot be reconstructed with complete assurance, it would appear most likely that a slowly developing pancytopenia was the essential and primary lesion and that coincident with each period of marked neutropenia there was an exacerbation of the existing gastro-intestinal infection. Such an interpretation would be in accord with clinical experience. It may also be argued that the infection was primary and resulted in the pancytopenia, but chronic infection rarely produces such a blood picture when the clinical evidence for this infection is so slight as to be unrecognized during life and when postmortem studies reveal only a relatively mild and localized infectious process. Infection, when overwhelming, produces exhaustion of the bone marrow with evidence in the peripheral blood stream of ineffectual and spasmodic attempts at regeneration. On the other hand, drowsiness, nausea, vomiting and fever are common enough accompaniments of extreme leukopenia and of pancytopenia and it is important to remember that in this latter disease the process does not steadily progress with smooth regularity, but rather by a series of remissions and relapses. It is important, further, to remember that all the formed elements are not simultaneously or equally depressed. As a rule the white blood cells suffer first, the red cell series second and the platelets last, although of course there are many exceptions to this general rule. Moreover, in the presence of leukopenia, even of the most transient sort, any existing infection may advance apace, to subside again as the primary defense against infection, the leukocytes, is reestablished. Taking all the evidence at hand, it would seem most logical to assume the presence of a progressing pancytopenia of unknown pathogenesis with a concurrent and secondary gastro-intestinal infection. In any event, extreme leukopenia and neutropenia in the presence of fever must be regarded as ominous, even though the phenomena may appear to be transient. We should be guarded in our prognosis, even though there be no anemia, remembering, as in the first case, that it takes time for such to develop. In brief, one cannot or should not interpret the whole





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PAIN IN THE REGION OF THE HEART

**Introduction.**—We shall deal in this paper with pain in the region of the heart that is not angina pectoris. The difference between pain or distress in the region of the heart and angina pectoris will not be discussed, because descriptions of angina pectoris can be found in many textbooks and a repetition is not needed.

The pain or distress in the region of the heart with which we are concerned not only is not angina pectoris, it is nearly always not a symptom of any organic disease, and is usually definitely neurotic. This statement will surprise very few. Physicians generally are familiar with the fact that pain in the region of the heart, even when it is of great severity, may be a neurosis. Nevertheless, we find that such pain, when encountered clinically, is so disturbing that it frequently causes physicians, particularly when they have it themselves, even though they are technically familiar with cardiac neurosis, to believe that the pain must be an indication of organic heart disease when it is not. The need for correct diagnosis is clear. There is a vast difference in the treatment of cardiac neurosis and cardiac disease. We could cite many case histories to show that errors of judgment in either direction may be disastrous. In this connection, we find that minor errors in diagnosis and treatment are often caused by a failure to appreciate that neurotic pain in the region of the heart may occur coincidently with organic heart disease. In fact, neu

roses are proportionately higher among those who have organic heart disease. Cardiac cases naturally have their attention directed toward and their anxiety aroused by the action of their hearts. Often, for example, a patient with mitral stenosis consults a specialist not because of symptoms due to the mitral stenosis, mitral stenosis may give no subjective symptoms whatsoever, but because the patient, knowing of the heart disease and its dangers, develops neurotic symptoms suggesting to all concerned an alarming situation. We also believe that, in spite of its importance, cardiac neurosis has been neglected. We seldom find it demonstrated in clinics or discussed at scientific meetings. It is a confusing topic and, therefore, perhaps avoided. We believe a discussion of it is in order.

**Terminology**—People suffering from vague symptoms, including pain in the region of the heart, which we nowadays definitely label neurotic, symptoms which tend to be confused with symptoms of organic heart disease, have long been recognized. Terminology has contributed to the general confusion concerning them. The inept term "functional heart disease" was formerly used to classify these cases and indeed we find it still used at times. During the World War these cases were vigorously studied, and this term was abandoned. The names "soldier's heart," "disorderly action of the heart," "effort syndrome" and most apt of all, "neurocirculatory asthenia," were applied to them. We will use this last term for the remainder of this article, abbreviating it to its initials, N C A. This term is generally somewhat familiar.

A distinction has been made by some observers between "cardiac neurosis" and "N C A" on the basis that in the former there is no objective evidence of cardiovascular disturbance. We believe it is inappropriate to try to make such distinction since our cases grade evenly from one class to another and individuals change their symptoms so that one would have to reclassify them from time to time. We would refer to N C A including those patients who would be called "cardiac neurosis" by those who wish to attempt a distinction.

**N. C. A. Among Soldiers**—Study during the war was forced by military and economic necessity. In England alone, at one time, 30,000 soldiers were in hospital supposedly com-

pletely disabled by N C A Physicians found themselves unprepared for these vast numbers of disabled young men with symptoms referable to the heart. The disorder did not resemble clearly anything with which they were familiar in civil practice

In brief, the disturbance was as follows soldiers who had it typically found themselves unable to carry on because of exaggerated feelings of extreme fatigue, they fell out of line of march and dropped at drill Though the symptoms differed in individuals, in general they complained of stabbing or tearing pains at frequent intervals, usually below the heart, rarely throughout the chest or down one or both arms Their hearts raced often at a terrific rate, sometimes more than 150 beats per minute If exercised on a flight of steps, or by 100 hops, their pulse rates did not return to within 10 beats of the preexercise rate after a two minute rest, they thus showed a poor response to effort Their blood pressure might be unobtainable when they first stood up, but within a few seconds or minutes would climb to a high systolic level, often with a relatively low diastolic level. Some fainted suddenly and remained unconscious for as long as twenty minutes They trembled so that some could not stand at attention, and had a sense and appearance of anxiety, of "impending calamity" They were breathless on slight exertion and spoke of a sense of suffocation, tachypnea was the rule even at rest. It was noted that their hands, feet and ears tended to be cyanosed, their extremities were cold and they sweated freely Of course "myocarditis" was the first diagnosis considered But direct examination of the heart showed no familiar signs of heart disease in the vast majority of cases and it was found that rest was bad for them while exercise helped the majority of them After a six weeks' course of graduated exercises and drill, roughly 20 per cent of these soldiers seemed able to return to full duty, 20 per cent appeared completely disabled, while the remainder could carry on some degree of duty Furthermore, these individuals never developed heart failure, no matter how breathless or exhausted they became No matter how severe the heart pain they never died. So myocarditis as a cause of the symptoms had to be rejected

Hyperthyroidism was clearly suggested by some of the



symptoms—rapid heart, tremor, increased fatigability. But the patients never developed clear signs of toxicity referable to the thyroid gland, and this possibility was also rejected.

No disease appeared to be closely associated with the condition. The most that one could say was that the incidence of chronic infections, in particular tuberculosis, was somewhat higher among these N C A's than in the general population. To be sure, N C A symptoms in some cases occurred for the first time or were aggravated by *convalescence* from acute disease or injury. So the effect of organic disease or physical trauma in initiating the symptoms could not be ignored even though it was clear that organic disorders or their late effects could not account for the great majority of the cases. The symptoms were the same where there was no apparent cause, or when they followed pneumonia, rheumatic fever, trench fever, battle wounds, shell shock, a drunken debauch, promotion, demotion, or bad news from home.

Five years after the war it was found (2) that 33 per cent were improved or well, 32 per cent had become worse. The condition of the remainder was stationary. This must not be taken as a guide for prognosis for N C A in civil life. Any familiarity with the severely disabled N C A soldiers shows the unfortunate fact that they are more secure if they remain disabled. Feeling their inadequacy, they dread to be pronounced well and forced to take care of themselves. Reassurance can have little effect. And indeed one can only reassure them half-heartedly. There is no certainty that they will succeed in being well if they try.

Follow-ups have shown that these N C A's were good life insurance and operative risks.

**N. C. A. in Civil Life**—It was through the study of soldiers that a solid, though inadequate, basis was established for the understanding and handling of patients with N C A encountered in civil practice. For a few years after the war, occasional reports and studies of this condition appeared, but for the past fifteen years it has been seldom dealt with in lectures or medical publications. We are forced to turn to the older descriptions for reference and we do not often recognize in them the condition we now encounter, for individuals who match the wartime cases in severity of signs and symp-

toms are now rarities. This may be because in civil life we rarely have anything analogous to the war as a cause of sudden and tremendous psychic shock among relatively young people and one can usually more readily escape from the severe tensions that do come in civil life. The symptoms of N C A as encountered today are less dramatic and, at the same time, less clear cut than the war cases. Nevertheless, they are often as disabling and sometimes the symptoms are as severe as ever.

The symptoms of civilian N C A are so various and vague that a thorough description would be difficult and undesirable. We find they are best described by illustrative cases presented against the background of their social and economic environment. We will later give such cases. Certain symptoms, however, occur so consistently that we will mention them. Of course, "heart pain" it grades in severity from a merely uncomfortable sensation or consciousness of the region of the heart or of the heart beat to precordial soreness and stabbing or pinching pain, sometimes of great severity. Such pain is by itself strong evidence of N C A. A complaint of breathlessness which really consists of sighing or a sense of inability to get enough air in the lungs, is also a clear sign of N C A. The precise value in diagnosis of other common symptoms and signs, such as great fatigability, breathlessness, tremor, cyanosis and tachycardia or poor response to effort is much less.

Curious case histories could be given where violent dyspnea or uncontrollable tremor or repeated fainting or complete helplessness from sudden sense of weakness were the outstanding complaints of cases severely disabled and suspected of heart disease, though the symptoms were purely neurotic, and were relieved by proper treatment. But such cases are comparatively rare. The most common outstanding complaint of the N C A today is some degree of pain in the region of the heart.

#### CASE REPORTS

Case I.—This patient is a forty five year-old busy surgeon who married rather late and has 2 small children. His father died of angina. The patient has frequently made a correct diagnosis of cardiac neurosis on his own patients nevertheless, he reported for examination with a look of despondency and weariness and placing his hand beneath his heart said, "I'm done. Angina."

He also complained of precarious sleep and a general sense of fatigue and numerous minor symptoms. Physical examination was negative except for a left inguinal hernia. He had had this for a year, shortly before the onset of his heart pain. It had prevented him from exercising, with the result that he had gained greatly in weight and was in "poor condition." He had, however, "always kept putting off an operation." He feared that he would have an embolus and die. He was advised to take a three months' vacation. There was improvement but only for a few months. A year later, he consented to the hernia operation. As soon as he recovered, his symptoms disappeared and he began to engage in active athletics. He has remained well for several years, though on questioning says that he has little echoes of his pain when especially worried. And, like many physicians, believes that eventually he will die of angina. Many do.

**Case II**—This is another physician, thirty-two years old, married with one child, who has been engaged in practice for five years, and through unremitting hard work is now succeeding. He has a good family and past history and no vices. He states that "for the past several months, I have frequently had a sharp stinging pain just under my heart, lasting a few seconds. I am sleeping badly. My wind is not as good as it was. I have been staying up late working and have stopped regular exercise during the last 2 years and have gained a lot of weight. I have never had rheumatic fever, but will you listen to my heart?" The examination was negative, and when he had been reassured and put on a proper schedule of hours for sleep, exercise and diet, his symptoms vanished. When asked several years later about these symptoms, he failed to recall that he had had them or that he had consulted one of us.

**Case III**—This patient is a healthy, attractive young woman of twenty-seven, the mother of one child. Her husband had left home to develop an artistic talent. He stayed longer than was expected. There were rumors of unfaithfulness on his part. The patient developed disturbing heart pain and consciousness of her heart beat which frequently was very rapid and forceful. There was breathlessness, easy fatigability and sleeplessness. These continued in spite of reassurance and a hygienic régime until she obtained a divorce with a financial settlement and retired with her child to live with her parents. Even then, there were milder recurrences until she was married to another, but since that time she has remained well.

**Case IV**—This patient is a psychiatrist of seventy-two years, charming and intelligent, who had lived a successful life without special hardships, illnesses or disasters. He stated that "I awakened frequently this last winter, and am conscious of my heart beating hard at times and of a sense of soreness around the precordium coming and going for days at a time. On occasion, I have the sensation that I am suffocating and desire to take a full breath. I am fatigued. I come to you to see if I have heart disease or a mother-in-law complex." He did not have evidence of heart disease, he did have a mother-in-law, aged ninety-two, who had come to live in his home and who was a source of increasing anxiety, but he also, though past the age of retirement, was continuing his work and lectureship from year to year, while constantly before him was the unexpressed question, "when shall I break?"

The neurotic symptoms disappeared with explanations and he resumed work with comfort. But the inevitable break came without warning a few years later with an entirely different set of symptoms.

**Case V.**—Again we are dealing with a physician, a teacher and consultant of forty, who has never been sick and states that he is not nervous. There have been no disasters in his life, he has a happy home several children and is successful in his profession. For a few months, he had noticed growing fatigability and breathlessness at his accustomed tasks and stabbing pains and a sense of soreness around the heart. Physical examination revealed no abnormality. He was reassured and discussion resulted in the idea that he was not getting enough exercise or rest. This was corrected but no improvement occurred. He then gave up smoking, in which he had indulged heavily and still he was no better. Finally his teeth were x rayed, three badly abscessed teeth were found and removed and within three or four days he experienced complete and lasting relief from his symptoms.

**Case VI.**—This woman now over fifty was seen by one of us ten years ago as the eighth consultant on her case. She was married, had 2 children and her environment was pleasant and easy. She had a normal inheritance except that a grandmother had been a cardiac invalid for thirty years. She herself had been kept out of school for a year when fourteen years of age with "anemia and myocarditis," but otherwise had had no significant illnesses. Her 2 children were born within two years of her marriage. Twenty years ago following her second and last pregnancy, she began to suffer from frequent attacks of severe stabbing pain over the precordium, together with consciousness of the heart beat. Her heart rate, whenever taken was found to be 120 beats per minute or over. There was weakness, easy fatigability and breathlessness. In addition, she suffered from vague digestive disturbances. These symptoms had persisted to the date of this examination. Her symptoms were such that she was only able to be up about six hours a day and felt that she had to be driven everywhere she went. She supervised her home and children but could do no work. She had no particular relaxations although she read a good deal. Her life with her husband was apparently congenial.

Her physical examination was quite negative, except for the tachycardia and some acrocyanosis. Treatment proved unsuccessful. A recent report from her family physician stated that her condition is still unchanged.

**Case VII.**—This patient is a thirteen year-old girl. Since the death of her father from angina when she was eight years old she and her mother had lived with a grandmother. During this time she has slept with her mother. The patient's catamenia commenced six months ago. Her symptoms extend over this six-month period. She began by disliking school, she trembled and felt faint and breathless at meeting people. She had soreness around the heart and frequent stabbing pains. Her heart raced at times. She dreamed dreams of the anxiety type frequently. She would hardly allow her mother out of her sight. One night, while her mother was attending a club meeting, she experienced an attack of heart pain so severe that a physician was called at once. He told the mother that he feared the child was suffering from rheumatic heart disease and that she would have to remain in bed for an indefinite period of time. Treatment by digitalis, vitamins and heliotherapy was given, but the symptoms became worse. A grave prognosis was given. The mother gave up all outside activities and devoted nearly every moment to her child.

The symptoms increased There were tantrums, fainting spells, blurring of vision and transient hemianopia The child had written poems for years, the poems had grown more mature as she grew older She continued to write, but now the content of her poems reverted to nursery rhymes

During the six months of her illness the grandmother had scolded the child and mother persistently, advising the mother not to spoil her daughter, to go out more and not to stay home and act as nurse When the physician was appealed to, he was distinctly apprehensive regarding the child's heart and insisted on complete rest (The physician, an experienced and able practitioner was not a poor diagnostician He was faced with a situation which again and again is found alarming by other able men)

Physical examination of this child was negative In spite of the severity of the symptoms and the difficulties of the situation, brief but unreserved discussion of the case with mother and patient together was followed by almost complete relief of symptoms and a return to normal living which has lasted for a year

**Discussion** —These above cases are chosen as typical The essentials of each are found in many others With the possible exception of Case V, none had any organic disease which could directly cause the symptoms, and all had sound cardiovascular systems In regard to most of them, factors in their lives producing anxiety states could be readily ascertained, although these factors had not been appreciated by the patients themselves Thus in one patient, Case I, it was an unsuspected dread of death from a needed but postponed operation, in another, Case III, a disturbance in her relationship with her husband, a third, Case IV, was apprehensive of the breakdown of old age, while a fourth, Case II, was in poor physical condition from overwork and under-exercise and sleep In Case VII an intricate and demanding attachment to her mother and jealousy for her attentions led to a state of complete invalidism at adolescence Only in Case VI, the sole one which did not respond to treatment, are the factors producing the psychic disturbance hidden In handling N C A's in general, it is not often necessary to resort to the radical therapy of such workers in abnormal psychology as Freud and Adler, but it is by no means wise to dismiss their theories as never applying In the more serious and resistant cases, such as Case VI, therapy along these lines may offer the only hope of relief One wishes that this patient (Case VI) had been analyzed

Focal infection, as in Case V, appears definitely as an exciting cause now and then, and effective treatment is dependent on its removal But focal infection is not demonstrable in

the majority of instances, and attempts to cure all by finding and removing obscure possible foci of infection repeatedly end in failure

Thus, the ordinary *wear and tear* and *vicissitudes* of life with their resulting *anxiety* states, *bad habits* of living, and, to some extent, in a few *inheritance* appear as the exciting factors in most cases. N C A may occur at all ages in both sexes, in all social conditions and among those with all degrees of mental ability. These individuals are usually not constitutionally "neurotic" unless we apply this term extremely widely. It is very common among physicians. Most of the patients get well.

The diagnosis of N C A rests on the recognition of the peculiar nature of the described symptoms. It does not depend on the exclusion of organic disease. It is not made by physical signs or tests.

No matter how elaborately we develop routine physical examinations and laboratory tests, the diagnosis of this common condition can only be correctly made from the personal judgment of an enlightened physician. Though in the great majority of cases the diagnosis to an experienced physician is easy, there are occasional cases that make even those who deal with these cases daily wish to shift the responsibility, and that keep us awake nights. We do not often worry for fear we may be overlooking a serious heart disease. Pain in the region of the heart can, of course, be caused by pericarditis. It may in rare instances be caused by pressure from a greatly enlarged heart, though cardiac enlargement as a rule causes no pain. But, aside from these, pain such as we are concerned with is not caused by obscure heart disease. But there are rare, sometimes serious organic diseases, that can give pain in the region of the heart that is not angina and that neurosis may simulate. Following are some of these rare diseases that, in our experience, have caused severe pain in the region of the heart. The principal lesions, not cardiac, *above the diaphragm*, which we have found in our private consulting practice as a cause for precordial pain are mediastinal, lung and esophageal tumor or diverticulitis, diaphragmatic hernia, pulmonary embolus, and cervical arthritis. *Below the diaphragm*, disease of the stomach, gallbladder, duodenum and pancreas. One some-

times reads of obscure chest pain which is labeled "pleurodynia," as though this was a specific disorder. We have never allowed ourselves to make such a diagnosis. Patients frequently believe and are encouraged to believe that pain in the region of the heart is due to pressure from gas in the gastrointestinal tract. This explanation serves to distract the patient's mind and to relieve apprehension. But it commonly causes cribbing and belching and resort to various remedies, not always harmless. And, sometimes, the result is a real discomfort from gas pressure. We should remember that pain in the region of the heart is nearly always neurotic. Gastrointestinal discomforts are common symptoms among neurotics. Bad habits, cathartics, cribbing, unnecessary dosing are easily induced.

Because of the similarity between the symptoms and signs of N C A and those of hyperthyroidism, the latter condition should always be considered and eliminated, if necessary, by a basal metabolic rate determination. It is often wise to take the basal metabolic rate on an evident N C A in order to convince the patient that hyperthyroidism is not present.

N C A as seen today is treatable and the prognosis, on the whole, is good. The great majority of patients get well quickly, often with no more therapy than reassurance. A small proportion, possibly 10 per cent, tend to be prolonged with a tendency to recurrence. A few remain fixed for years, perhaps for life. But even the most prolonged and intractable cases sometimes suddenly get well. We cannot handle them all alike, though some need following indefinitely, many are cured at once with reassurance and should not be encouraged to remain under surveillance, which, in itself, may be poor therapy.

The general principles of treatment are reassurance, repeated as often as needed and as convincingly as possible, and a régime of diet, rest, exercise and work suited to the individual. Drugs, in general, are not indicated, digitalis and the other specifically cardiac drugs do no good. Occasionally, in selected cases, sedatives may be used temporarily to combat excessive nervousness or sleeplessness. But, in our opinion, the use of sedatives ought usually to be considered as an evasion. Explanation and reassurance rather than narcotics are

in order. Any reasonably correctable defects, such as infected teeth, should be corrected.

They should have time for sleep and time for rest and relaxation during the day. But they should not be put to bed. Sometimes a long overdue vacation is helpful, but, in general, it is possible and desirable to get the patient well *while* at work, regulating the daily régime so that the patient does not *over work* and does stubbornly follow the rules of bodily and mental health in spite of doubt and discomforts. Diet should be adjusted to maintain the patient's weight within proper limits. Vague digestive disturbances, mentioned above, frequently require a nonirritating diet. Habits of cribbing, and poor bowel management often need correcting. On the whole, elaborate schedules of graded exercises such as were developed for the war cases has proved neither necessary nor especially helpful in civil practice. It is exceedingly difficult to apply such schedules thoroughly to patients who cannot be observed and controlled like soldiers. Treatment of N C A by the more elaborate forms of psychiatry, such as we mentioned in discussion of Case VI, especially psychoanalysis, has been little tried as yet, but keeps suggesting itself as a logical possibility. Because of expense and time, psychoanalysis cannot be widely used by a cardiologist or an internist. And we should remember that we know that it is not necessary to resort to such heroic methods for satisfactory results in the great majority of cases. It is possible that in the future, the rare intractable cases will be recognized and come promptly under the case of a psychiatrist, while the cardiologist, becoming more versed in the technic of psychiatry, may be able to handle the usual cases in a more comprehending fashion. One hopes that more enlightenment from modern psychiatry will enrich what we now cherish as hard won common sense in the treatment of these common neurotics and not lead us to costly errors, as have other theories that explained the neuroses on the basis of some organic disease.

**N C A. Complicating Organic Heart Disease**—Finally, we should like to cite two cases with N C A and with organic heart disease. It must be remembered that patients with organic heart disease or, indeed, any disease, may in addition have N C A. These N C A symptoms may be the real cause



of a disability, and may be totally unrelated to the organic disease. We were surprised recently to find that 20 per cent of a large series of young women with mitral stenosis seen in private practice complained of heart pain which was exactly like the pain described by patients with sound hearts who had N C A

**Case VIII**—The patient is a young woman, aged twenty-three, who was three months married and three months pregnant. She had no knowledge of any cardiac defects. She led a normal life with much exercise. She stayed up all one night at a dance, drank a little. Then during sexual intercourse became breathless, orthopneic, and raised pink-stained sputum. Orthopnea and breathlessness with signs of congestive heart failure continued for several hours and cleared. Seen the following day, her physical examination was negative except for mitral stenosis. Since then the patient has led a symptomless life with careful restrictions for twelve years, and has had 3 successful pregnancies. Following the death of 1 child by accident, she developed *severe* pain for the first time in the left chest in front, particularly below the heart and in the axilla. She became conscious of her heart beat, which was rapid. She frequently felt a desire to take a deep breath. She had anxiety dreams.

The physical examination showed no evidence of congestive failure and no change in her heart condition. Reassurance and explanation diminished at once the severity of her symptoms without change in her régime.

**Case IX**—This patient, a woman of forty-two, who had rheumatic fever in her youth, but following this led to a normal life, was married and had 2 children. Following the birth of the second child, "she did not regain her strength," but suffered from breathlessness at her accustomed tasks and complained of a great sense of fatigue and of sleeplessness and precordial pain. She was seen in consultation at this time (twenty years ago) by an able cardiologist, now retired, who found mitral stenosis and apparently interpreted this as the cause of her complaints and stressed merely the necessity of a cautious régime on her and her husband. For twenty years the patient was up only a few hours a day, rarely went out, and was almost constantly conscious of her heart. Distressing precordial pain was the most prominent of her many symptoms. She never developed congestive failure. Suddenly, after twenty years of cardiac neurosis and no heart failure, without warning, she developed a right hemiplegia, probably from an embolus broken off from a thrombus formed behind the stenosed valve. She recovered partially from the paralysis, but her personality clearly changed. She became cheerful, fearless, free from complaints. There was no more mention of consciousness of the heart and heart pain. She struggled about the house doing more work than she had done at any time for the past twenty years, and remained up all day. This state continued until the patient was lost sight of several years later.

### Discussion —Case VIII explains itself

Case IX shows the results of a misinterpretation of symptoms. If the cardiologist who first saw her had appreciated that her complaints were not due to her mitral stenosis, but

to cardiac neurosis and given proper treatment, she probably would have been improved or cured of the N C A. The abrupt cessation of her N C A symptoms following the embolus offers a chance for speculation to those addicted to speculation on these matters. Did the embolus by causing organic change in her brain cells change her personality? Or did the obvious physical handicap of her partial paralysis provide her with a better excuse for invalidism (or outlet for her maladaptation if we prefer) than did her less obvious neurotic symptoms, and did these N C A symptoms disappear because she no longer needed them? At any rate, we are satisfied for the purpose of this paper that for twenty years the patient, though possessing mitral stenosis, really was disabled by poorly treated N C A and that, following the onset of an additional and organic disability, she lost her N C A, did more, and was happier. Such sudden changes in personality in prolonged N C A appear to occur at times without any recognizable cause, psychic or structural.

**Summary**—Several cases complaining chiefly of pain in the region of the heart have been presented and discussed. The facts have been stressed that pain or distress in the region of the heart that has no association with angina pectoris or coronary occlusion, is common. It is rarely organic. It is usually neurotic. It may be disabling. It is successfully treatable in the vast majority of cases. We have discussed the general management of such cases.

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### THE CURABILITY OF POLLEN HAY FEVER

PRESEASONAL treatment for pollen hay fever offers a cure, provided that the proper pollen extract is used, careful tests are made and judgment is employed in the manner of treatment. Two very important facts that are essential to successful pollen treatment are that the patient must be accurate in his statement as to when and how long he has hay fever symptoms, and that the physician must know what plants are shedding pollen at that particular time in that patient's environment. A third important fact is to test the patient very carefully and accurately with those pollens which are prevalent during the patient's hay fever season. Another essential is a proper procedure of treatment and, finally, extraneous conditions must be taken into consideration for each patient. These important considerations will be discussed in detail.

**Hay Fever Seasons**—The time of year or season when the patient has pollen hay fever falls into one or more of three periods, namely spring, early summer, and late summer or fall. Naturally, the time of year that these seasons occur varies for different parts of the United States and more especially for foreign countries. For example, in New England the early summer season, during which the grasses pollinate, extends from the middle of May to the middle of July. Farther north this season is delayed two weeks, and as one goes south this season gradually advances. In Florida, a grass is in pollination in January, in Texas, cedar trees pollinate in January, in Venezuela, grasses pollinate in January. Rainy seasons in some parts of this country and foreign countries as well as cold winters in this country and Europe naturally permit of a resting period for pollination.

During the spring hay fever season, which in most parts of this country extends through March, April and May, the trees pollinate in a series. Since each tree completes its pollination in from one day (the pine) to several days (the oak) a patient must be sensitive to the pollen of more than one tree in order to experience much pollen hay fever at this season.

During the early summer season, May, June and July, the various grasses pollinate and they may cause hay fever for a period of six to eight weeks. The grass pollens are the cause of hay fever in from one quarter to one third of all cases of hay fever and the symptoms are severe. It is noted that in May some of the late pollinating trees and some of the early pollinating grasses coincide, therefore, these two seasons overlap. After the grasses have finished pollination there is in most localities a brief respite from pollen hay fever, it is a period of two or three weeks before the late hay fever season starts.

In the late summer, August, September and early October, the compositae, more especially the ragweeds pollinate. These are a profuse pollinator, cause severe hay fever symptoms for six or eight weeks and are responsible for about two thirds of all the hay fever cases.

Occasionally patients are sensitive to pollens that occur in all three seasons, more often to those pollens that occur in both early and late summer, or early summer alone, and most frequently to the pollens of late summer only. Certain grasses, for example, Bermuda grass, which pollinates after it has been cut two or three times a year, may be in pollination during the late hay fever season. Corn, which belongs to the grass family, pollinates, depending upon when it is planted, from late May to the middle of August. Although the pollen of corn does not contaminate the air which one may breathe, it does fall upon the silk and husks of the ear. Therefore, a patient who is sensitive to the grass family may have attacks of hay fever from husking corn during August and September, when the compositae are in pollination, and without tests ragweed pollen would be blamed for the cause.

All plants as regards pollens, are divided into two classes, namely those whose pollens are borne by insects and those that are borne by the wind. A more practical division is,

those that are fragrant and pleasing to the eye and those that have little or no fragrance and little or no beauty. Those plants which have fragrance and beauty are cultivated and are insect pollinated, rarely cause hay fever. The pollen is heavy or sticky and is not dislodged by wind or air currents while in their normal condition. When such blossoms are cut from the plants and kept in a vase for a few days they may dry and considerable amounts of pollen may be blown about by drafts. However, such instances cause symptoms of only a few days' duration. Wind borne pollens naturally lodge everywhere, even on blooms of non hay fever causing plants so that the act of smelling of a rose in early summer may cause the inhalation of grass pollen, or in the fall, of ragweed pollen. Consequently, the patient's statement as to the cause of his hay fever may be very misleading. Roses are rarely the actual cause of hay fever and the same is true of golden rod, both of which are often suspected. The pollen of golden rod and daisy is sticky and does not blow about and consequently these do not cause hay fever in their natural habitat. The same is equally true of asters, golden glow, zinnias and fruit trees, etc.

The wind borne hay fever-producing pollens are from plants that have inconspicuous blooms with no fragrance nor beauty, no qualities to attract insects and they produce nothing that insects desire. Examples of this type are non fruit bearing trees, the grasses, ragweeds, tumble weeds, etc.

**Geographical Distribution of Pollens**—A complete geographical distribution of hay fever pollens is out of the question in this paper. However, a brief survey may be of interest and helpful.

*In the East Coast States*—As far south as North Carolina the spring season of hay fever, during March, April and May, concerns the willow, maple, oak, birch and poplar trees. The early summer season, from the middle of May to the middle of July, concerns only the grass family. June grass pollinates usually from the middle of May to the middle of June. Very few patients, however, are sufficiently bothered by this grass to warrant treatment. All of the other grasses ripen at about the same time, and since timothy is one of these and has an abundant pollen, treatment with timothy pollen seems to protect sufficiently against the other grass pollens. In the fall

hay fever season only ragweed needs to be considered, the dwarf or small variety north of Connecticut and both the small and giant south of Connecticut

*The Central States*—In Kentucky, Ohio, Indiana, Illinois and Wisconsin, blue grass, timothy grass and lambs quarters are important from May to September and the ragweeds and careless weed from July to August. In Chicago, blue grass and orchard grass cause most of the hay fever during the early summer and the ragweeds and lambs quarters in the fall. The spring season is of little importance.

*The Mississippi Valley States*—All have similar seasons and similar pollens as stated above with the addition of Bermuda grass and Johnson grass. Throughout the States of Minnesota, Iowa, Mississippi, North Dakota, South Dakota, Nebraska and Kansas, blue grass, timothy grass, lambs quarters, ragweed, careless weed and sage brush are the most important causes of hay fever.

*Southern District*—In Oklahoma the maples pollinate the latter part of February, the cottonwood tree in April, and both cause some hay fever. Bermuda grass pollinates from the middle of May until frost and is a contributing cause in one third of all hay fever cases. Water hemp is a very heavy pollen producer and is a very common cause of hay fever in Oklahoma and in the eastern and southern parts of Texas, Nebraska and the southern part of South Dakota, Iowa and Michigan. From the middle of August until the first of October the ragweeds are important causes of hay fever.

In Arizona and the southwest, the season of pollination begins the last of January and continues through November. Furthermore, after the annual rainfall there may be a different flora or different causative pollens from one year to the next. Rabbit bush and shad scale cause spring hay fever, Bermuda grass and June grass cause hay fever in the spring, summer and fall. The Amaranths, rather than the ragweeds, cause the fall hay fever. Outside of the irrigated districts the pollen seasons depend upon the annual rainfall. In the irrigated valleys there is a continuous hay fever season for nine months. Cottonwood pollen causes hay fever in February, the ash trees in March, Bermuda grass begins to pollinate early in April and continues for nine months. In the latter half of the

season the pigweeds and *Amaranthis* cause hay fever and, as already stated, Bermuda grass is still in pollination. In south western Texas the cedar tree causes hay fever during December, January and February, Bermuda grass during April, May and June and again from the latter part of August to November. In northern Texas the grasses and ragweed pollen cause most of the hay fever.

*The Mountain States*—In Colorado the cottonwood trees cause hay fever in May, blue grass and grama grass in May, June and July, and lambs quarters and the ragweeds from June to frost. In the region about Colorado Springs cottonwood trees cause early hay fever and Russian thistle, sage brush and ragweed the remainder of the summer. In Nevada, during April and May, ash, olive and black walnut trees cause hay fever from April to October. Johnson grass and Bermuda grass cause much hay fever and in addition, during July and August, rye grass. From July to October Russian thistle is most important and careless weed and red root are less important as causes of hay fever in the late summer. In Montana there is little spring hay fever from the trees, more hay fever in May and June from the grasses and 60 per cent of all cases have hay fever from July to frost and this is caused by Russian thistle, sage brush and poverty weeds.

Oregon is divided by the Cascade Mountains into two distinct areas as regards pollens. To the east of these mountains June grass pollinates in May and June, bunch grass, wheat and tall rye grass during June and July and in the late summer and fall Russian thistle pollinates from June to September. Sage brush pollinates from June to August and *Atriplex* from June to September. West of the Cascade Mountains are several river valleys and the pollen flora is varied. However, since 96 per cent of all hay fever patients in Oregon have the early or midsummer type of hay fever, which is caused by the grasses, enumeration of the various floras is of no interest. In Utah, during the spring season from April to June, a few patients have hay fever from shad scale. The summer season from mid July to September is the most important in that 83 per cent of the patients have hay fever at this time. The principal cause of hay fever at this time is Russian thistle. In California the pollen flora is so varied in different districts



that it is not possible to give a detailed report Black walnut, orchard grass, rye grass, June grass, Bermuda grass, red root, pigweed and mug wort are hay fever-causing plants which are common throughout the state In the Sacramento and San Joaquin Valleys olive trees and Johnson grass are important. In the region about Los Angeles and Pasadena careless weed is important About San Francisco Bay sage brush is important In Southern California during January and February the pollens of black walnut, English walnut, live oak, scrub oak, cottonwood and cypress are prevalent During March, April, May and June the various grasses pollinate and of these the most important are Bermuda grass, orchard grass, red top and fescue Bermuda and ray grass pollinate practically throughout the year During July, August, September, October and November, first the wild rye species, Johnson grass and the *Atriplexes*, then follows the western ragweed and cockle bur, and finally the *Artemisia* family

*Foreign Countries* —There seems to be no late summer or fall hay fever outside of North America and the chief cause of hay fever, namely, ragweed, is not known In Argentina there is a tree season in early spring and a summer season due to the grasses, which pollinate during January and February In England, France and Germany the chief causes of hay fever are the grasses and the season is similar to that in New England In Spain there are two grass seasons, early spring and late summer, and two thirds of all cases are caused by the grass family The olive tree also causes considerable hay fever in Spain

**Collection of Pollen** —Pick the flowers when they are just ready to shed the pollen, spread them upon sheets of smooth paper in a closed room and allow them to dry Much pollen will be found free upon the paper The dried anthers with the pollen inside or sticking to them can be separated from the pollen by grinding them slightly with a mortar and pestle in small amounts of carbon tetrachloride The carbon tetrachloride with the suspended pollen is strained through cheesecloth to remove the gross fragments, and then it is allowed to fall upon smooth filter paper, while the carbon tetrachloride runs through into the flask The same sheet of filter paper is used several times until a large amount of

pollen has collected. The filter paper is then allowed to dry, and the pollen forms a cake. This dry pollen is separated with care from the filter paper and put into a clean, dry and tightly corked bottle, where it will keep indefinitely. Pollen collected in this way is quite free from dust, is uncontaminated by other pollens, and seems to be more or less sterilized by the passage through carbon tetrachloride. Pollen can be purchased from reliable firms that deal in biological products, but they must be of the species indigenous to the patient's environment.

**Preparation of Pollen Extract**—There are many different ways of preparing pollen extracts for use in the testing and treatment of hay fever, and all of them seem to give satisfactory results when used by the worker who devised them.

A method in general use is that of Clock, which is to extract the pure pollen grains in 66.6 per cent glycerol and 33.3 per cent saturated sodium chloride solution. Another method is that of Coca's, the dry pollens are treated with ether until all the fats are removed, then the pollen is extracted with the following solution: sodium chloride 0.5 per cent, sodium carbonate in such concentration that 10 cc. of the final fluid equals about 3 cc. of tenth normal alcoholide and carbolic acid is added in a final concentration of 0.4 per cent. Alles and Lawson extract the dry pollen grains with occasional shaking in a fluid containing glycerol, sodium dihydrogen phosphate and disodium hydrogen phosphate. This extract is isotonic in salt content, has a hydrogen ion concentration within the limits of normal blood sera, seems to contain all of the salt and water soluble active substances present in pollen grains, and is stable.

The method used by the writer is to extract 1 Gm. of dry pollen in 88 cc. of normal saline with frequent shaking for twenty-four hours, then 12 cc. of absolute alcohol is added to make a 12 per cent alcoholic saline solution and extraction is carried on with occasional shaking for another twenty-four hours. To the extracting fluid carbolic acid is added to make a final 0.4 per cent. This alcoholic, sodium chloride, carbolic acid solution is used for further dilutions of the pollen extract.

**Methods of Testing for Pollen Sensitization.**—*The*

*Cutaneous Test* —A number of small cuts, not scratches, each about  $\frac{1}{8}$  inch long, are made on the flexor surface of the forearm. The cuts are made with a sharp scalpel, with an even pressure, so that they are deep enough to penetrate the skin without drawing blood. Sometimes in testing infants or small children the tests are made on the back. On each cut is placed a very small amount of the dry pollen to be tested. When all of the pollens have been applied to the cuts, a drop of tenth normal sodium hydroxide (4 Gm NaOH to 100 cc of distilled water) is added to dissolve and to admit of its rapid absorption. Great care should be used not to carry pollen from one cut to the next and not to contaminate the fluid. At the end of half an hour the pollens are washed off and the reactions read. A positive reaction consists of a white area or urticarial wheal, often irregular in shape and with outrunners or pseudopodia, surrounded very often by a flushed or rosy area.

*The Intradermal Test* —This consists of the injection into the skin of minute amounts of pollen extract, usually 0.01 cc. It consists, essentially, of a parenteral injection into the body of a foreign protein. The technic is rather difficult, since the volumes to be injected must be exactly the same in the control as in the diagnostic tests, for accurate comparison of the size of the reactions. The intradermal test is so very sensitive that false reactions or pseudoreactions are a common occurrence. The tendency to multiple or group reaction to botanically related pollens, is common so that the intradermal method is sometimes unsatisfactory as an indication of the specific pollen which causes the hay fever symptoms. The most serious objection to the use of the intradermal test is the occurrence of severe local or constitutional reactions.

All plants belong to some biological family of which there are numerous members. Consequently, some plants are so closely related to each other that all members of that family will give a positive test whether cutaneous or intradermal, even though only one member may be the cause of hay fever. To illustrate this a patient, who has hay fever in the fall of the year that is caused by ragweed pollen, will react more or less positively to daisy pollen, which is present in the air in midsummer, and which, because it is so heavy, it does not blow

Before treatment is instituted it is essential that the patient be tested for various strengths or dilutions of the particular pollen to which he may be exposed. The original pollen extract may be diluted so that when tests are done with various strengths or dilutions the degree of sensitivity of the patient may be established. When this is done it is usually found that the pollen which is the cause of hay fever gives a positive test in the greatest dilution or with the least amount. Whereas other members of the pollen family, to which the patient is not exposed, require larger amounts of the pollen to give a positive test and some members of the family may react very little with very large amounts.

**Preseasonal Treatment**—Unless the patient is tested with graded amounts of the pollen protein such as various strengths or dilutions it is not possible to know the initial dose for treatment or when to start treatment. Without these graded tests the first dose of treatment may be too large, thereby causing a distressing reaction, or the first few doses may be unnecessarily too weak to be of value. Furthermore, knowledge of the positiveness of the patient to various strengths or dilutions of the pollen protein is an important guide in treatment. For example a patient reacts as follows: 1:100 is 4+, 1:500 is 3+, 1:1000 is 2+, 1:5000 is 1+, 1:10,000 is  $\pm$ , 1:20,000 is doubtful, 1:40,000 is 0. It is safe to begin treatment with 3 minims or 0.2 cc of 1:40,000. If no reaction occurs from this dose and none would be expected, the next dose would be 3 minims or 0.2 cc of 1:20,000, and no reaction would be expected. The third dose would be 3 minims or 0.2 cc of 1:10,000 and although no reaction would be expected it is known from the tests that from now on treatment should be slower and not increased so rapidly, therefore, the

fourth dose would be 5 minims or 0.3 cc of 1:10,000. The fifth dose would be 3 minims or 0.2 cc of the 1:5000 dilution, the sixth dose would be 5 minims or 0.3 cc of 1:5000. Since there is a greater jump from the 1:5000 to the next dilutions of 1:1000 than there was in the preceding dilutions, it is necessary to give two more doses of the 1:5000, namely, 7 minims or 0.4 cc and 9 minims or 0.6 cc. Although a mild reaction may follow the latter doses, a distressing reaction would not be expected. However, should one of these doses cause a large, red, hot, local reaction at the site of treatment or any constitutional reaction, the dose that was responsible should be repeated before proceeding with the schedule. Since the next dilution, namely, 1:1000, caused quite a reaction in the tests, we are forewarned to proceed cautiously. Therefore, with this 1:1000 dilution, in order to be as safe as possible, three doses are given, namely, 3, 4, and 5 minims or their equivalent in the metric system. With no reaction following these three doses, and none would be expected, it is then proper to give the 1:500 dilution in doses of 3-4-5-6-7 minims or their equivalent in the metric system. This schedule calls for 16 treatments without any repetition. In 9 cases out of 10 an excellent result would be expected.

The above schedule is often varied to fit the degree of sensitivity of the individual patient, with consideration of the ability of the patient to tolerate an increase in the amount of pollen injected, as judged by the effect of each preceding treatment. Very sensitive patients, who require treatment with the 1:160,000 or even higher dilutions, are frequently unable to take the larger amounts of pollen extract dilutions before the time of onset of the symptoms, but they receive a great deal of benefit from treatment with the dilutions which they are able to tolerate. Less sensitive patients are sometimes treated with a 1:100 dilution of the pollen extract in amounts of 0.1 cc or 2 minims, 0.2 cc or 3 minims, and 0.3 cc or 5 minims. Since the best results are obtained when treatment is given at weekly intervals, and since 16 treatments are outlined, it is best to begin treatment sixteen weeks before the usual onset of hay fever symptoms. Treatment given at five-day intervals offers nearly as good results. Treatment that is given at more frequent intervals does not produce as satisfactory results.

Successful preseasonal treatment depends upon the following (1) to start the course of treatment early enough to complete the schedule a week or ten days before the usual time of onset of the symptoms, (2) to test by the cutaneous method with the actual pollen extract dilutions which are to be injected in treatment, (3) to adjust the initial amount to the degree of sensitivity of the patient, *i. e.*, start with the dilution which gives no reaction, but is next higher to a dilution to which the patient gives a slight reaction, (4) to increase the amount or strength of the injections as rapidly as the patient can tolerate them with no more reaction than a slight and transient local irritation about the site of the injection (swelling less than the size of a fifty-cent piece, with surrounding flush, of less than twenty four hours' duration), (5) to repeat any amount that causes any marked local or any systemic reaction, (6) to inject the material subcutaneously, not intradermally, intramuscularly, or intravenously

**Coseasonal Treatment.**—This method of treatment differs from the preseasonal method only in that treatment is started just prior to or after the onset of hay fever. The results are not nearly as satisfactory as those obtained from the preseasonal method. Furthermore, it is hazardous because the patient is being exposed to pollen in the atmosphere at the time he receives treatment, and there is no way of estimating how much pollen the mucous membranes are absorbing at the time of treatment. In those cases where the patient is sensitive to several different species of pollens it is of some advantage to treat with some pollens coseasonally, provided the preseasonal treatment can be given with only a part of the pollens. If the patient applies for treatment after his hay fever has started and the season is a long one, it is well to give the coseasonal treatment a try, if it benefits, the patient is the gainer, if it fails, it can be stopped.

**Preseasonal Combined with Coseasonal Treatment** — When a patient applies for treatment four to ten weeks before the usual onset of symptoms, a combination of the pre-seasonal and coseasonal treatment may be given. The treatment is carried out as outlined for preseasonal treatment up to the time the patient begins to have hay fever symptoms. From then on the increase in dosage is adjusted in accordance with

the condition and reactions of the patient. During the season the patient may not tolerate increased amounts of the pollen extract but may obtain much relief from repeated doses of a quantity that he can tolerate.

The results from the combination of preseasonal and coseasonal treatment are not as good as from the preseasonal treatment alone, but are much better than from the coseasonal treatment alone.

**Perennial Treatment**—This method really consists of giving more or less preseasonal treatment, then continuing during the hay fever season with as much treatment as the patient will tolerate and after the hay fever season is finished and the time has arrived to again start the preseasonal treatment.

The aim of this method is, after a certain amount of immunity has been established, to hold or preserve as much of this immunity as possible until another course of preseasonal treatment can be started for the purpose of a further increase of immunity, etc. The advantage of this treatment over pre-seasonal treatment alone is that between courses of the latter there is a more or less decrease in immunity during the interval of no treatment. From the patients' point of view the inconvenience and expense of such a prolonged series of treatments may offset any advantages this method may have over the pre-seasonal method.

**Seasonal Results of Pollen Treatment**—With the careful adjustment of treatment to each patient, as has been detailed by making tests with the same pollen dilutions that are to be injected in treatment and by using the proper pollens, preseasonal treatment offers much benefit to 85 per cent of cases. In districts where the pollen flora is not extensive, such as in New England, 98 per cent of patients are greatly benefited. Over a period of fifteen years the writer finds that the average results from his treatment is that 15 per cent of patients have no hay fever, 30 per cent have practically no hay fever, 40 per cent are at least 75 per cent improved, 10 per cent are 50 per cent improved, and the remaining 5 per cent are not benefited. In other districts where the pollen flora is more extensive, such as in Arizona, where Bermuda grass and June grass cause hay fever during the spring, sum-

mer and fall and in addition the amaranths cause fall hay fever, the results would not be quite as satisfactory because of the necessity of using several pollens in the treatment at the same time and because the grass season is so long

From coseasonal treatment alone the results are not very good, but the combination of preseasonal and coseasonal treatment offers results that approximate those from preseasonal treatment. Perennial treatment gives equally good results

Cutaneous tests with pollen dilutions at the end of a course of treatment are much less positive than at the beginning of treatment. But this greatly decreased sensitivity does not hold over completely until the next course of treatment is instituted. However, at the beginning of a second course of treatment, the cutaneous tests are as a rule much diminished over those which prevailed at the beginning of the preceding course of treatment. Therefore, with each course of treatment there is a gradual diminishing in the cutaneous tests and there is a gradual improvement in the symptomatic results of succeeding treatments

**Permanent Results from Preseasonal Pollen Treatment.**—In my own experience with my own pollen extracts permanent relief has been obtained in one third of those so treated. Only a few patients have been permanently cured following one or two seasons of treatment and the majority of cures followed three, four, five and six successive preseasonal courses of treatment. If the number of those who were treated from three to six successful seasons were considered, the percentage of cures would be nearly 50 per cent. In fact, 55 per cent of all those treated four successive seasons, and 65 per cent of those treated five successive seasons have had permanent relief. About 5 per cent of the whole number have had treatment for seven or eight seasons and although they obtained complete relief from each season's treatment, their cutaneous reactions have not shown any permanent decrease and the few who have omitted a season's treatment at various times had considerable hay fever that season. Therefore, it would seem that this 5 per cent of the total would probably never be permanently cured. There are two guides or indices that tell when an apparent cure is reached and treatment may be safely omitted. One is, when the cutaneous reaction to the



causative pollen has become negative and the other is, that the pollen reaction must show a considerable decrease if not negative, and the patient should have had two seasons of complete relief from hay fever while under treatment

About 20 per cent of those who have had permanent relief from pollen hay fever were never completely free from symptoms while under treatment. They were patients who had more or less symptoms throughout the year from causes and conditions other than pollens. This establishes the fact that pollen hay fever patients may have symptoms from causes other than pollen, that the pollen cause may be cured but there still may be more or less symptoms which must be explained on some other basis

The positiveness of pollen tests in these cases usually diminishes with each succeeding course of treatment until the tests become negative or there is a very great reduction in the sensitivity. When this occurs it is logical and usually safe to stop treatment. Causes and conditions which produce symptoms, even though the pollen cause has been cured, will be discussed in succeeding paragraphs

### **Complications in the Treatment of Pollen Hay Fever**

—In the complicated cases of pollen hay fever treatment is not as simple as in the pure pollen cases and it is this group of patients that perplexes the practitioner and the handling of these cases is best accomplished by the experienced or specialist. These complications may be perennial or seasonal

*Perennial Complications*—A mild vasomotorrhinitis, a sensitive mucous membrane of the nose that is manifested only by sneezing and watery discharge, and the susceptibility to so-called "frequent" head colds, any of which conditions may be due to sensitization to some protein other than pollen, and more often due to a mild bacterial infection, may be present in a patient who has pollen hay fever. The patient may have become quite accustomed to the perennial condition and may seek relief only from the seasonal hay fever, therefore, a careful history is important. Occasionally a patient is slightly sensitive to some food protein or to an animal protein, not enough to cause symptoms throughout the year but during their hay fever season the combination of these with the pollen to which they are sensitive is sufficient to cause mild symp-

toms in treated cases Similarly face powder, which is used more extensively in the warm months, may cause symptoms Mechanical irritants such as soap, powders, dust, train smoke, gases, perfumes, etc., may cause little trouble throughout the year, but more trouble when the mucous membranes are already somewhat irritated by pollen Abnormal conditions of the mucous membrane may permit aggravated symptoms when these membranes are irritated by pollen.

*Seasonal Complications*—Since the cereals belong to the grass family, a patient who is sensitive to both the grass and late fall pollens, may have some hay fever in the fall from husking green corn, the corn pollen is present in the husks Insect pollinated flowers, when kept in the house as a bouquet, dry out, and their pollen may then blow about or be inhaled If these plants belong to the same family as the ones to which the patient is sensitive, they may cause some irritation Some patients are sensitive to certain foods which are eaten only during the summer and these may cause hay fever or in a treated case they cause brief attacks of sneezing and lacrimation following their ingestion Ingestion of beers, wines, and hard liquors often is immediately followed by an attack of hay fever of a few hours' duration in a pollen sensitized individual.

It is often difficult to differentiate between a summer head cold and an attack of hay fever, whether the patient is or is not sensitive to a pollen Sudden changes in temperature provoke nasal secretion and fits of sneezing in many individuals, and those reactions may resemble the symptoms of pollen hay fever In the spring and in the autumn, when the days are warm and the nights are cool and damp, many individuals, whether sensitive to pollens or not, will have an attack of sneezing and watery nose on arising in the morning and again in the evening until more clothing is put on For the conditions mentioned in the paragraph, a vaccine often greatly benefits or relieves

It is not uncommon to test patients who complain of hay fever at a time which corresponds more or less accurately to some pollen season, and find them negative to all proteins, including pollen proteins A careful history, however, will often solve the problem. Usually such patients do not have con

tinuous symptoms, but instead, a day or two of symptoms may alternate with a day or two of freedom. Their symptoms are frequently worse on cold, damp, rainy days when, of course, there is no pollen in the air, and they are much better or completely relieved on warm, sunny days, when there is abundant pollen. These are usually of bacterial cause and vaccines are indicated. Without tests and a careful history, the physician would suspect, and often would treat the patient with the pollens that were prevalent at that season with no benefit.

The odors of fragrant flowers, face powder perfumes, soap or any pungent odor, the inhalation of gases, dust, train smoke, burning leaves or cloth, etc., often irritate a mucous membrane that is already irritated by pollen and have no effect at any other season.

**Conclusion**—It is evident that a careful history should be taken from all hay fever cases with especial attention to the time of year that they are effected and to other influences or complications. It is essential to know to what wind-blown pollens the patient is exposed, tests will tell to what pollens the patient is sensitive, but the physician must know to which the patient will be exposed. Before treatment is given tests should be made with different strengths or dilutions of the causative pollens. Such tests will help to select the proper pollen since it will react strongest, they will tell when to start treatment since the number of treatments will be defined by these tests and the tests are a guide to the different doses to be given. Treatment should be intensive with as few pollens as possible. It is not advisable to treat with a mixture of pollens from very closely related plants that pollinate at the same time because intensive treatment with one of them will protect against exposure to the group. Definite directions and a well advised schedule of treatments may have to be altered in any particular case, the schedule may call for too strong a dosage in one case or too weak in another. Such directions and schedules are a guide to proper treatment and if they are determined by previous tests they are usually satisfactory. Directions and schedules that are formulated without a previous test on the patient to be treated are apt to be valueless.

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### THE PRACTICAL MANAGEMENT OF CONGESTIVE FAILURE

CARDIAC failure of the congestive type is one of the most common problems encountered in medical practice. Although a familiar subject, it is none the less full of interest on account of the variety of its manifestations and of their response to treatment. To be sure, the main principles of treatment are well enough understood but their practical application to patients with congestive failure provides many opportunities for the display of resourcefulness on the part of the clinician. It is a condition where minor tactics often play a decisive rôle in the outcome and it is to these homely practical details that we shall chiefly devote our attention today. The discussion will be grouped around *general measures*, *drug therapy* and *mechanical measures*.

**General Measures —Rest —**In the treatment of severe grades of congestive failure, rest must mean a great deal more than mere confinement to bed. Its real meaning is best understood in terms of metabolism by saying that the metabolic rate should be maintained as close to the basal level as practicable. In order to achieve this, there must be a minimum of muscular activity, of mental and of digestive activity and an attendant strong enough to move the patient should be constantly available to spare him any unnecessary exertion. While acutely ill he must, of course, be fed, bathed and shaved and, during this stage, the bowels are best emptied by enema, preferably by the two way enema or low colonic irrigation. The latter

possesses the advantage of not requiring the use of a bed pan, so that the patient does not have to be moved. The bed pan is a physical and mental hazard to the bed-ridden cardiac. For many it is less of a strain to be moved onto a commode beside the bed. The stools must be kept soft with cathartics so that there is no expulsive straining.

The optimum position of the cardiac patient in bed will depend upon the degree of orthopnea to which he is subject. A few with extreme orthopnea will be most comfortable in a chair. A new "cardiac bed" in which the foot lets down while the head comes up is a great comfort for these patients. In determining how long to keep a patient with congestive failure in bed, one has to bear in mind that the longer he remains in bed the more skeletal muscle tone he will lose and, with it, peripheral vascular tone. This will tend to increase the strain on the heart when he first gets up. For this reason and on account of the danger of hypostatic pneumonia, it is advisable to get aged patients sitting up in a chair just as soon as possible. For the same reason, gentle massage and passive exercises are worth-while procedures during convalescence.

Mental rest is also an important objective in the treatment of cardiac failure. If the condition is acute, the patient is apt to be the prey of anxious thoughts and disturbed sleep. Under these circumstances morphine is indicated as much for the comforting euphoria which it induces as for the reliability of its soporific effect. Later on, of course, the main dependence for sleep must be placed on less habit-forming drugs such as the barbiturates or chloral hydrate. Restless patients often feel better during the day if the "edge" is taken off by a mild sedative such as phenobarbital,  $\frac{1}{2}$  grain three times a day.

The sick room must be as restful and quiet as possible and kept at an even temperature. Visitors should be strictly limited and should be cautioned against allowing the patient to do much talking.

*Diet*—The diet of a cardiac should consist essentially of concentrated low residue, high carbohydrate foods given in small amounts at frequent intervals. This accomplishes several purposes. It avoids undue strain on the heart from overloading the stomach, it reduces the amount of bowel residue

to be expelled, it furnishes glucose in readily available form to replenish exhausted glycogen stores in the myocardium, and it minimizes the stimulation of metabolism from specific dynamic action. In the critical stages the carbohydrate may be given in the form of concentrated dextrose solution intravenously. For oral use fruit drinks sweetened with glucose or lactose are employed. The Karell diet (800 cc. of milk per day) is useful on account of its simplicity and its low caloric content. As Master has shown, the basal metabolic rate of a cardiac patient may be lowered to as much as minus 30 by a low caloric diet. Easing the load on the heart in this way may prove useful in the treatment of obstinate cases of congestive failure.

The fluid intake must, of course, be rigidly restricted. Not more than a quart a day is a good general working rule. It is well to ration it out in small amounts at stated intervals during the day so that it will not all be squandered before noon. Salt also should be limited because of its action in binding water in the tissues. In most cases a restriction of salt to what has been put into the food in the kitchen will suffice, but an obstinate few will require a completely salt-free diet. The substitution of potassium chloride for sodium chloride as a table salt is worth while in patients with chronic edema. The potassium chloride will furnish almost as much savour without the water binding effect of sodium chloride.

Oxygen therapy is indicated if cyanosis becomes marked. The oxygen tent or chamber is the method of choice but if not available, the nasal catheter will usually prove satisfactory. The disadvantage of the nasal catheter method is not that it does not deliver oxygen in sufficient concentration to the nasopharynx but that it is apt to be uncomfortable for the patient. The chief sources of discomfort are insufficient saturation of the oxygen with moisture so that the patient's throat is burned, and the use of catheters which are too stiff. If due attention is paid to such details the patient will often experience a feeling of marked relief when oxygen is started and may drop off to sleep. Objectively there is usually an improvement in the color and the respiratory and pulse rates are slowed. Improvement in intraventricular conduction during oxygen administration has been demonstrated and suggests that the

efficient functioning of the myocardium itself may be enhanced by this procedure

**Drug Therapy — *Digitalis***—A word has already been said about the important place which the opiates and the sedatives occupy in the treatment of congestive failure. Of the specific cardiac drugs, digitalis, of course, still ranks foremost. Digitalis therapy has been somewhat confused by the myriads of proprietary preparations which have appeared on the market in recent years. These preparations vary widely in potency and a few still make unwarranted claims in regard to not causing "gastric irritation" and nausea. The nausea of course is due to an effect on the vomiting center and not to any local effect in the stomach. A digitalis preparation which will not produce nausea in large doses is not a potent preparation. Occasionally one encounters a patient who has been conditioned against digitalis by having been nauseated by it in the past. To such a patient the smell and taste of digitalis is nauseating and if they are to take it by mouth it must be given in the form of a coated pill. It is very seldom that one finds a person who is really sensitive to digitalis.

In determining the dosage of digitalis to be administered to a given patient the Eggleston formula of 15 grains (0.1 Gm) of the powdered leaf or 15 minims (1 cc) of the tincture for every 10 pounds of body weight is a useful guide. There is so much variation in individual tolerance to the drug that even if all preparations were of fixed potency, no formula for dosage could be more than a rough index. In general, the tolerance to digitalis is proportional to the total metabolism. For this reason, children, active ambulatory patients and patients with fever or hyperthyroidism require relatively larger doses—sometimes twice as much per unit of weight—as compared to the aged, the inactive bed ridden and those in whom a significant proportion of the weight is due to inert edema fluid. Since it is impossible to predict exactly how much a given case will tolerate it is well to approach the estimated total optimum dose gradually. For example, if it is desired to digitalize a 150 pound man in twenty-four hours, the estimated total dose would be  $\frac{150}{10} \times 15 = 225$  grains. This would be divided up as follows

|                  | <i>Individual<br/>dose</i> | <i>Total<br/>dose.</i> |
|------------------|----------------------------|------------------------|
| Initial dose     | 9 grains                   | 9 grains               |
| Three hours      | 6 "                        | 15 "                   |
| Six hours        | 3 "                        | 18 "                   |
| Nine hours       | 1½ "                       | 19½ "                  |
| Fifteen hours    | 1½ "                       | 21 "                   |
| Twenty-one hours | 1½ "                       | 22½ "                  |

Inquiry as to anorexia or nausea should be made before each dose is given and the drug discontinued at the first sign of toxicity. If no effect whatsoever is noted, it may be continued in doses of 1½ grains three times a day until an effect is produced. If the patient has had an uncertain but apparently inadequate amount of digitalis, he may likewise be given 1½ grains three times a day. This dosage is also useful in digitalizing ambulatory patients who are not under close supervision, as in the average person one week of it gives approximate digitalization. In regard to digitalis dosage the dictum of Withering published in 1785 still holds good. He wrote "Let the medicine, therefore, be given in the doses, and at the intervals mentioned above, let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels, let it be stopped upon the first appearance of any one of these effects." Other indications for discontinuance of the drug are the appearance of yellow vision and very frequent extrasystoles or bigeminal rhythm.

The electrocardiogram may yield further information in regard to the effect of digitalis on a given patient. It may show, by a specific change in the contour of the T waves, plain indications of a drug effect long before toxic signs appear. It may also give evidences of toxic action not readily detectable by other means of examination (partial heart block, frequent extrasystoles or periods of complete heart block in auricular fibrillation). In children, however, the electrocardiogram may remain normal in the presence of digitalis poisoning.

Some of the drug houses, in order to assure the consumer of a potent product, now dispense their digitalis products in terms of cat units. The cat unit is approximately equal to 1½ grains (0.1 Gm) of the digitalis leaf (U. S. P.) which is standardized in frog units. For convenience and precision of dosage the pill prepared from the whole leaf is very satisfactory for routine oral administration. Occasionally it is necessary to



administer the drug parenterally, the indication being more often gastric disturbances than the necessity for extreme haste in digitalization. It is here that some of the purified extracts of digitalis have a place. The most powerful of these is crystalline ouabain, which is one thousand times as potent as standard digitalis. One mm. of ouabain intravenously is the maximum dose in an adult and should be divided into at least two injections given one half an hour apart. Strophanthin is a related compound of approximately equal potency derived from another source. These powerful drugs must be used with greatest caution, particularly if there is any question as to the amount of digitalis the patient has had just previously. Satisfactory preparations are also available for intramuscular use. Rectal administration is less satisfactory because one is never sure exactly how much has been absorbed. Dosage is the same whichever way the drug is administered. The average daily maintenance dose of digitalis is  $1\frac{1}{2}$  grains but some individuals cannot take half this dose and others will require three times as much.

By far the best results from digitalis are to be expected in the group of patients suffering from auricular fibrillation with rapid ventricular rate. The chief benefit in these cases is the elimination of the premature, inefficient, ventricular contractions. No such dramatic results are seen in auricular fibrillation with slow ventricular rate or in normal rhythm. The contrast is indeed striking, but should not obscure the fact that digitalis is usually of definite, although limited value, in the latter group.

*Diuretics* —The importance of diuresis *per se* in the management of congestive failure can not be too strongly emphasized. Edema is much more than an inert burden of water, for in many ways it acts as a vicious aggravating factor to increase the work of the heart. In the lungs it causes respiratory distress and brings about a lowered oxygen tension in the blood with all the resulting train of altered function in vital organs, including the myocardium. In a limb it has been shown to increase the minute circulating volume of blood, again throwing an extra burden on the heart. Its presence in the liver, the kidneys, the intestinal mucosa, indeed in the myocardium itself, interferes directly with the function of

those organs. Edema, therefore, is to be regarded as a harmful complication to be eliminated as promptly and as completely as possible.

Of the specific diuretics we need discuss only the two most important groups—the mercurials and the purines. The most satisfactory mercurial on the market today is salyrgan. This drug combines a powerful diuretic effect with a minimum of toxicity. Being a mercury compound it is contraindicated in the presence of advanced kidney disease but appears to exert no deleterious effect on the normal kidney. I have had occasion to use it twice a week over a period of three years in a patient with congestive failure and a mild degree of arteriosclerotic nephritis without any aggravation of the renal condition. It possesses the advantage over the milder purine diuretics of greater reliability of action and—because it is given intravenously or intramuscularly—of not upsetting the stomach. The dose varies from  $\frac{1}{2}$  cc. in children to 2 cc. in adults. Preferably it is given intravenously, but if veins are not available it may be given intramuscularly in the deltoids. If it is deposited subcutaneously or in edematous tissue where absorption is slow a slough will result. A diuresis usually appears within a few hours and persists for twelve to twenty-four hours. The dose may be repeated after three days. The drug is more effective if the patient is mildly acidotic, so that if no diuresis follows the first injection, a course of ammonium salts should precede the second. These salts possess diuretic properties themselves. Ammonium nitrate is preferable to ammonium chloride because it is less irritating to the gastrointestinal tract. It is best given in  $7\frac{1}{2}$  grain (0.5 Gm.) enteric coated pills—three pills every three hours for 6 doses on the day before and on the day of the injection. With this adjuvant a hitherto ineffective mercurial will often prove active.

The purines possess distinctly less diuretic effect than the mercurials but they have the advantage that they can be taken by mouth. They are indicated in the milder cases where the mercurial has proved ineffective. Caffeine is the mildest diuretic of the purines and too weak to be of clinical importance. The most commonly employed are theobromine and theophyllin. The former is given in doses of  $7\frac{1}{2}$  grains (0.5 Gm.) of the pure alkaloid or 15 grains (1 Gm.) a day for

two or three days of theobromine sodium salicylate three times a day Theophyllin is given in the same manner in doses of 4 grains (0.25 Gm) three times a day Both of these drugs have the disadvantage of frequently causing gastric irritation, nausea and vomiting The purines may be used in conjunction with the mercurials to obtain an enhanced effect A new preparation called "mercururin," which combines the two in one ampule has proved to be a very powerful diuretic—the two drugs seeming to have an additive effect

**Mechanical Measures** — *Venesection* — Venesection is indicated if the venous pressure is high, as evidenced by engorged neck veins, or if there is acute pulmonary edema If there is no anemia from 400 to 600 cc of blood should be withdrawn

*Tapping* — Abdominal paracentesis is worth while if the ascites is considerable in amount (more than three liters) and may be followed by a sustained diuresis Thoracentesis is justified if the amount of pleural fluid is sufficient to embarrass respiration Removal of subcutaneous fluid by means of Southey tubes is useful in obstinate cases

*Surgical Measures* — In the last few years total thyroidectomy has been advocated in the treatment of certain obstinate cases of congestive failure The procedure is radical and technically difficult It requires the closest sort of organized teamwork between internist, surgeon and nursing staff The patients must be picked with care, the ones most suitable for the operation being those who are edema-free in bed but who can not get up without developing congestive failure Under ideal conditions, a fair proportion of such cases will be improved by total thyroidectomy It is not likely that it will be frequently resorted to

The proper management of a case of congestive failure involves quantitative measurements of the effectiveness of the various procedures employed The best rough index is a chart of the daily fluid intake and output When the patient can be moved a weight chart is an invaluable check The rapidity of weight loss in diuresis is sometimes astounding, reaching as much as 10 pounds in a day The chart may also demonstrate the loss of edema "hidden" in the tissues which gave no physical signs of its presence

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### SYRINGOMYELIA—DIAGNOSIS AND TREATMENT

**Case Reports.**—*Case I*—A housewife of forty-eight was admitted to the Massachusetts General Hospital and gave the following history about four years previously she had stepped off a slowly moving train and had felt a slight snap in her neck, and pain and tingling radiating down both arms. She

(Detail E V Massachusetts General Hospital — 6  
POSTERIOR ANTERIOR

1 Temp. impaired roughly over same area as pain (stage downward) 2  
3 (line upward) Cold better determined than hot.

1 Thel. left side Temp. 4++  
Impaired (from jaw down)  
2 Rt. lds. same  
3 Both legs fairly accurate

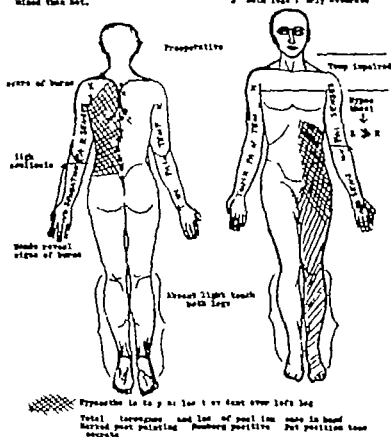


Fig 173—Case I Distribution of motor and sensory changes

had had similar sensations occasionally in the legs also. For about a year before admission there had been complete loss of the sensation of pain in the right arm so that she had frequently burned herself. More recently the sense of touch and position sense had been impaired in the arms, and she had become slightly unsteady on her feet.

Neurologic examination confirmed her subjective complaints (Fig 173). There was definite atrophy of the shoulder girdle. All deep reflexes were exaggerated on the right, and the left Babinski was equivocal.

x-Rays of the spine showed a forward displacement of the fourth cervical vertebra. Lumbar puncture showed normal dynamics and the fluid was normal except that the protein was increased to 58 mg. Iodized oil injected into the cistern could be seen to pass the cervical enlargement in a thin stream.

A cervical laminectomy was performed. The entire cervical cord was found to be reduced to a thin-walled sac filled with spinal fluid which had evidently caused an atrophy of the walls of the canal by pressure and so had permitted a pathological fracture. The sac was incised along the midline posteriorly over a distance of about 3 cm opposite the fifth vertebra. It was lined with glistening ependyma, and the cavity evidently communicated with the fourth ventricle.

The patient made a good operative recovery, and was relieved of pain. Her arms improved, and she was able to get about. In the course of a few months, the weakness of the legs recurred and progressed in spite of x-ray treatments, so that the patient was helpless when last seen a year after operation.

*Case II*—A mechanic of thirty-two was admitted to the Massachusetts General Hospital on account of a "hammer" deformity of the left middle finger. A plastic operation on the tendons was contemplated, but neurological examination showed a characteristic "dissociated" sensory loss, scoliosis and facial asymmetry. The patient was slightly ataxic, and it was learned that the scoliosis and unsteadiness had been present since infancy. This was before the days of either x-ray treatment or operation for syringomyelia, and all that could be done was to amputate the last phalanx of the affected finger, which was in the patient's way.

*Case III*—A man of fifty-five was admitted to the Boston City Hospital following an attack of faintness. He had lost consciousness without obvious cause four times during the previous two and a half years. He had been having pain in both arms for five years, and some tingling in the left hand for a year and a half. He had lost much weight. There was atrophy of the deltoids and of the hands, especially the left. The pain was, at times, severe enough to require morphine. There was a Horner's syndrome. All modes of sensation were impaired in the left hand, but only pain and temperature in the right. There were exaggerated reflexes, a Babinski sign, and loss of position sense in the left foot. Lumbar puncture showed a partial block and increased protein.

Cervical laminectomy revealed two fusiform enlargements of the cord, one at C<sub>4</sub> and the other at C<sub>6</sub>. Both were opened, the lower one contained about 30 cc of xanthochromic fluid, the upper was solid. The walls were dark and rough. Following operation the pain was less severe, but there were no objective changes. The patient's symptoms gradually progressed and he died fourteen months later.

*Case IV*—A man of twenty-four was admitted to the Boston City Hospital complaining of weakness, stiffness and numbness of the right leg gradually increasing for three years. From seven to nineteen years of age, he had had attacks of unconsciousness with crude visual hallucinations. About a year before admission, his right arm also became weak and numb. Vision had

always been poor in the right eye. Examination showed facial asymmetry (Fig 174) scoliosis, scars of painless burns on the fingers (Fig 175), and



Fig. 174.—Case IV. Facies.

atrophy and fibrillation of various muscle groups of the shoulders and arms. There was bilateral clonus, Babinski's sign, and ataxia of the legs.

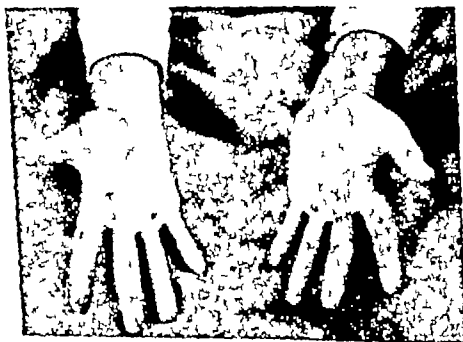


Fig 175.—Case IV. Painless burn of right hand, atrophy of hypothenar eminence.

There was a slight optic atrophy and a bilateral paracentral scotoma. Several lumbar punctures were performed, one of which showed 9 lymphocytes, another a protein of 83.

Several x-ray treatments were given, but the symptoms became worse rather than better. Finally, laminectomy was resorted to, and this disclosed an enormous cavity occupying the entire cervical cord, filled with spinal fluid. It was incised over a length of about 15 cm. The lining was a glistening white, and the walls nowhere more than 2 mm in thickness. The cavity appeared to communicate with the fourth ventricle. The patient made a striking improvement after operation, not only did the sensory signs regress, but motor power was greatly improved, so that the patient could use his hands, walk long distances, and drive an automobile. The operation is now four years ago, the symptoms have very gradually returned, but have not yet reached their original severity.

*Case V*—A man of twenty-eight entered the Boston City Hospital with the complaint that for three months his gait had been unsteady, especially at night. He also had a sense of coldness in the left arm and leg. Examination revealed asymmetry of the face, scoliosis, huskiness of the voice, and nystagmus in all directions. There was a loss of pain and temperature sense over the left side of the face, and also over the first four cervical and first and second sacral segments on both sides, without disturbance of sensation of touch. There was slight atrophy of left thenar muscles, and all deep reflexes were increased. The Babinski reflex was positive on both sides. Vibration and position sense was impaired in both feet, and there was an astereognosis of the left hand. Lumbar puncture showed normal dynamics and negative findings except for a protein of 58.

The patient was given x-ray treatment over the entire spine. In three months there was definite improvement, and he returned to work.

**The Diagnosis**—These cases, picked almost at random, may serve to indicate the fact that syringomyelia does not by any means present the stereotyped clinical picture which most textbooks describe. To be sure, a "dissociated" sensory loss in the arms and some atrophy of the muscles of the hand is the rule. Indeed, the symptom of painless burns from cigarettes (among women, flatirons and stoves used to be equally common agents) is practically pathognomonic. But the standard teaching that injury to the long tracts is rare, should be abandoned. Some degree of spasticity, ataxia or loss of vibration sense is extremely common, and may be the presenting symptom. Pain in the arms is also often encountered. Atrophy of the muscles of the tongue or face with fibrillation has, of course, long been recognized, and so has the presence of nystagmus, but the frequency of their occurrence has been underrated. The explanation usually given is that the cavity extends into the medulla, but it seems probable that involvement of the cervical cord alone may suffice to produce it. A Horner's syndrome may occur.

Two somatic manifestations are of importance, first because they are almost constantly present, second because they may be immediately evident on inspection, and third, because of their possible significance in the interpretation of the nature and course of the pathologic changes. They are facial asymmetry and scoliosis. The facies may be strikingly similar from case to case (Figs 175-177). Typically, the face is thin, the chin sharp, and the nose slightly out of line with the chin. One cheek is ordinarily more hollow than the other. The "bite" may be crooked. Pimples are common. Whether this facies actually is a "family resemblance" is an open question,



Figs. 176-177.—Facies of two other patients, whose cases are not reported here. Notice "family resemblance" rather long face, sunken cheeks, deep nasolabial fold, various slight asymmetries.

since we shall see below that the tendency to the disease is doubtless hereditary. It is perhaps more likely that both this and the scoliosis are the result of muscular imbalance, in turn dependent upon involvement of the grey matter. The fact that these manifestations may often be traced back to early childhood—as indeed the ataxia and some other symptoms may also be—is evidence that the underlying pathologic change is congenital.

Little emphasis has been placed upon *cerebral* symptoms, which have, however, been observed in so many cases that they can scarcely be dismissed as a coincidence. Syncope and



convulsions are the commonest, but others have been reported. It has seemed to me that a dependent, self-pitying attitude, sometimes combined with emotional instability and a tendency to blame others, was of frequent occurrence, but possibly this is merely a reaction to an affliction which is often progressive and crippling, and may occur in adolescence.

Visual symptoms are also encountered. Optic atrophy with enlarged blind spots is the only type I have observed personally, but papilledema has been reported. The possibility of confusion with multiple sclerosis and syphilis is obvious.

**Alterations Produced in the Spinal Fluid**—The following data are summarized from the book "The Cerebrospinal Fluid," now in the course of preparation by Dr. H. H. Merritt, by his kind permission, in a group of fluids from 31 cases of syringomyelia; the pressure was over 200 cm. of water in 7 instances, for an unknown reason. In 2 cases, a subarachnoid block was demonstrated. In almost half the cases (including these two) the protein was higher than the normal upper limit of 46 mg. Occasionally a slight increase in cells was found. On the whole, therefore, examination of the spinal fluid is of little aid in the differential diagnosis from multiple sclerosis and cord tumor.

**Etiology**—It has long been suspected, although on rather scanty evidence, that syringomyelia is the result of a hereditary defect. The disease may occur in association with other congenital defects and has been reported in two members of the same family. The observations of Ostertag,<sup>1</sup> that a similar condition exists as a recessive Mendelian trait in some strains of rabbits, lend a new weight to the theory. In these animals the lesions may vary from microscopic size to cysts which cause complete paralysis. In human beings also lesions of typical histology but too small to cause symptoms are a fairly common postmortem finding, usually in association with other neurologic diseases, for the spinal cord is seldom examined in subjects who have had no symptoms. It has been seen in this laboratory in association with spinal syphilis and myelomalacia, and has been reported with multiple sclerosis<sup>2</sup> and acromegaly.<sup>3</sup>

Alternative theories are that the cyst is the result of an as-

ceding neuritis or of a spontaneous hematomyelia dissecting up and down the gray matter. The fact the symptoms may be of insidious onset in childhood, and may progress irregularly or even regress, renders both improbable, as does the histology of the lesion. The cases in which an abscess of a finger has produced an ascending lymphangitis, and the signs of syringomyelia have then been discovered, may perhaps equally well be interpreted as instances of the increased danger of trauma and infection when the sensation of pain is absent from its sentry post. Hemorrhage into the gray matter may occur, and local pressure on the cord (as from a tumor) may cause necrosis chiefly in the gray matter, but in neither instance is a progressive process initiated. The symptoms of syringomyelia may often be first noticed, and possibly made worse, by injury, but close inquiry will almost always elicit evidence that the disease dates back to childhood.

**Pathology**—The lesion usually described is one which begins in the gray matter of the cervical cord, and gradually spreads upward and downward. The fibers carrying the sensations of pain and temperature are usually involved more than any other group, either in the commissure or in the posterior horn. It is doubtless for this reason that the sensory loss may be greater on one side than on the other. The fibers subserving the sensations of position, vibration and (probably) touch run directly from the posterior root ganglion into the posterior column without a synapse, and are, therefore, less often injured, but they too may suffer. An irregular invasion of the anterior horns accounts for the muscular atrophy. The process is practically always most intense in the cervical region, but may spread up to the pons and down to the lumbar enlargement. The gray matter is chiefly involved, but the white matter may be injured also, perhaps in part by pressure.

It is usually stated that in true syringomyelia the cavity is distinct from the central canal and fourth ventricle, and contains a yellow fluid. If the cavity communicates with the subarachnoid spaces, the condition may be designated as hydromyelia, and it is often implied that this is a relatively benign condition. The experience gained by surgical interventions makes it appear probable that there is no real distinction between the two. In only one of my own cases has

the cavity contained xanthochromic material, rich in protein. In the six others, it contained spinal fluid, and evidently connected with the fourth ventricle. There was, however, no particular difference in the manifestations or clinical course of the disease in the two groups respectively, in my own cases, and in others in the literature. Usually the cavity is lined with a glistening white ependyma if it contains spinal fluid, and with a rough gray or brown glial growth if it is discrete. In one of my cases, both coexisted. The cysts containing spinal are usually the larger ones, and as in the first case reported above, may actually distend the cervical canal. It is no wonder that pain is produced by pressure on posterior roots. One would expect that the Queckenstedt test would more often show a block. It is probable that the fluid wave may be transmitted through the thin sac wall.

Histologically, the new formed tissue is found to be composed of fibrous astrocytes. There is usually little evidence of active proliferation, few nuclei lie in the thick feltwork of fibers. Vessels are rare. Occasional accumulations of blood pigment occur. No real inflammatory lesions are seen in the cord, but a mild meningoencephalitis over the brain has been reported. So has hydrocephalus.

The gliotic tissue may undergo a gliomatous degeneration. At least, this is the current interpretation. It is possible that central tumors, and perhaps other processes, may produce cavities in the gray matter which are entirely secondary and not progressive. Further study is needed to settle this point.

**Treatment by x-Ray**—In every case, as soon as the diagnosis is made, roentgen radiation should be administered. It appears to be more effective early in the disease than later, and perhaps more should be expected of it as a preventive than as a curative measure. It is not universally effective. Improvement has been obtained in about 60 per cent of the cases reported in several series, but my own experience has not been as favorable. Some cases are definitely made worse by radiation. There is further the danger that excessive treatment will produce changes in the skin which may render subsequent operation difficult. It is, however, always worth trying, and may even be used as a diagnostic measure, for no other condition likely to be confused with syringomyelia is

likely to be affected favorably Multiple sclerosis, for example, is distinctly aggravated

**Operative Treatment.**—Atypical instances of syringomyelia may easily be mistaken for cord tumor, and doubtless many isolated cases have been operated upon since the early days of spinal surgery The first surgeon bold enough to recommend opening the sac was Elsberg,<sup>4</sup> as far as I have been able to learn A few subsequent operations are recorded, but the procedure remained a novelty until Poussepp reported two successful cases before the International Congress of Neurology in Paris in 1925<sup>5</sup> Since then a large number of similar operations have been reported, the majority of them



Fig 178.—Hands of a patient with syringomyelia (not reported here) to show contractures A Before operation B after operation

from Russia, where the disease appears to be unusually common<sup>6</sup>

In general, the reports have been favorable Most striking, both in the literature and in my own cases, has been the decrease of analgesia and anesthesia, and “before and after” charts have been frequently used as evidence of the efficacy of the procedure Unfortunately, it is seldom the sensory disturbances which drive the patient to seek relief The motor weakness in the hands and the injury to long tracts are less regularly improved, but sometimes definite benefit is demonstrable (Fig 178) It is difficult to form an estimate of the proportion of favorable results from the literature, for evi-

dently successes tend to be reported in greater numbers than failures. In the 7 cases which I have observed personally, substantial improvement was observed in 4, although in all of them there has been some progress of symptoms since operation. In two others a decrease of the band of analgesia resulted, which looked well in the patients' record, but did not materially improve their ability to help themselves. Juzelevskij, who reported the largest series on record, gives somewhat similar statistics, 16 out of 22 cases were improved.<sup>7</sup>

On the other hand, the operation has not proved as dangerous in my experience as it is sometimes alleged to be. There have been no deaths, and no separation of the wound edges, which has frequently been recorded. One patient suffered a slight increase in the ataxia of one hand, otherwise, the postoperative condition has been no worse when it has been no better than that before operation.

The question has often been raised—does the opening in the sac close again? Recurrence of symptoms has taken place in several instances, and in a case reported by Frazier<sup>8</sup> the cyst had reformed. To avoid reaccumulation of fluid, it has been suggested that a drain of fascia or rubber be introduced into the drainage opening. From the pathological point of view, this would seem ill advised. A foreign body in contact with nervous tissue invariably becomes encapsulated in a mesodermal scar, which is exactly what one would wish to avoid. The problem is better met, it seems to me, by making the incision the entire length of the sac, or at least as long as the laminectomy allows. In the majority of instances, the edges will then gape apart and collapse into contact with the floor of the cyst. Whether adhesions will form, and whether the pia will obligingly regenerate to form a false passage from the lumen to the surface, must be left to future observation to decide. It would seem *a priori* unlikely, but some cases remain improved years after the operation. This brings up two minor technical points. The first is, where should the sac be opened? Poussepp suggests through the posterior horn of one side. My own policy has been to incise where the sac is thinnest, but usually in the midline, and this has not led to noticeable ataxia of the legs. When a long incision (of several centimeters) is made, bleeding may be troublesome, as the

posterior spinal vessels are too small to clip or tie successfully and too intimately attached to the cord to coagulate as they lie. If, however, they are gently raised on a dural hook, a light cutting current may be used to seal them without injury to nervous tissue. Collateral circulation is sufficiently rich to make up for any loss of blood supply.

**Indications for Operation**—Weighing all of the considerations which have been enumerated, when should we recommend operative treatment? There is evidence that operation does not permanently halt the progress of the disease, and closure of the drainage opening is particularly to be feared if the sac is small. It is, therefore, not to be advised as a measure of prevention, which  $x$  ray treatment appears sometimes to be. Radiation should be given a trial first, therefore, probably in all cases.

*Pain* is usually an indication for operation. It is seldom relieved by  $x$  ray treatment, but usually yields to relief of tension within the sac. As pain is an important symptom of syringomyelia, the indication is an important one.

*Spinal block*, if it occurs, should probably prompt an operation. If there is an obstruction to the flow of fluid, the walls of the sac must inevitably be subjected to pressure, and this in turn is likely to be responsible for at least some of the symptoms. An increase in the spinal fluid protein is to be taken as presumptive evidence of block.

Finally, in many cases *economic disability* is a situation which justifies the pursuit of even remote chances of benefit. It is in this group of cases that the most marked and most gratifying improvement is obtained, and it is fair to hold such a possibility open even to extensively crippled patients.

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## CLINIC OF DR. STANLEY COBB

### MASSACHUSETTS GENERAL HOSPITAL

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#### CONCERNING FITS\*

If a patient greets you in your office with the complaint, "I have frequent headache," your mind runs rapidly over a list of possible causes, a shorter or longer list according to the extent of your experience. Many are rapidly eliminated as impossible or improbable in this patient. Nevertheless, days of study will be spent before the list of possibilities is cut down to a workable few. But if a patient greets you with, "I have fits, doctor," often your mind is filled with a vague concept of a "disease" called "epilepsy" inherited, deteriorating and hopeless. Such a concept frequently inhibits further intelligent research into the etiology of a particular case.

It is my contention that epilepsy is a simple, fundamental manifestation of nervous disintegration. "Disintegration" means here the loss of more or less of the functional harmony of the central nervous system. Integration is the main function of the central nervous system, it is the process of building up useful behavior patterns out of the many and varied stimuli that reach the cord and brain, physiologically it works by summation, facilitation, inhibition, long circuiting and coordination. The essence of the process is delay of incoming stimuli to allow for association and for reaction conditioned by past experience. Now this integration may be interfered with by physical or chemical injury to nerve cells, or by conditions which alter nerve function. Because I believe that a condition of interference with integration is essential to the production of fits, and because the interfering conditions are many and diverse, I believe that epilepsy cannot be called a disease.

\* Read at the meeting of the Suffolk District Medical Society March 28 1935 Massachusetts General Hospital



To illustrate this I have made a chart (Fig 179\*) enumerating 60 conditions associated with convulsions in man, some rare, some common. These 60 I have tried to explain on one or another physiological basis, and for this purpose have

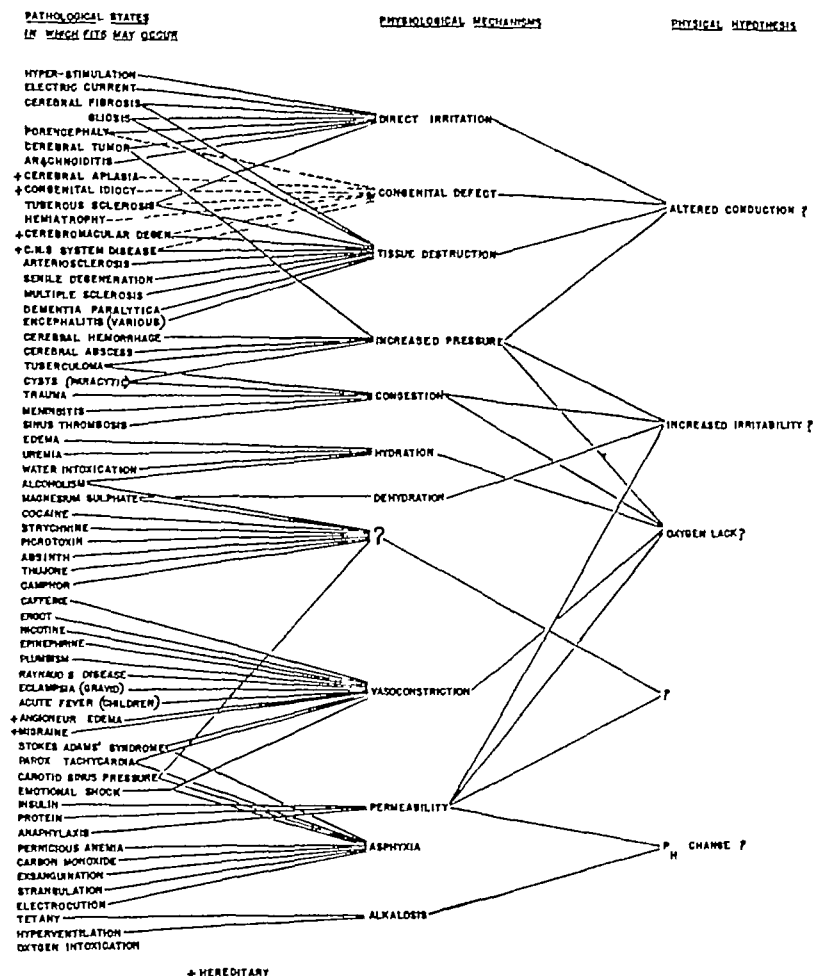


Fig 179

joined them by lines to 12 possible physiological mechanisms which have gone beyond normal limits and become pathological processes. These relationships are admittedly speculative.

\* A similar chart was published by me four years ago in the Arch Neurol and Psychiat, 27 1245, 1932. The present chart is a revised and enlarged edition.

For a few there is good evidence, for others very little. Even more speculative are the four "physical hypotheses" which make up the last column, the most reliable symbol here is probably the large question mark! But there is no use in gathering data if they are not classified, analyzed and thought about. So the speculation is justified that altered conduction of the nerve impulses, increased irritability of the nerve cells, oxygen lack of the nerve cells, or change in acid base equilibrium are probably important factors in many convulsions.

For the first two hypotheses we have the recent work of Gibbs, Davis and Lennox<sup>1, 2</sup> which shows by means of beautiful electro-encephalograms that epileptic seizures are accompanied by a change in the cerebral electrical potentials, this is recorded as a wave that has an apparently significant shape. Oxygen lack seems important because so many of the 12 physiological mechanisms may give rise to anoxemia, and because clinically, interference with circulation seems to be one of the surest methods of inducing loss of consciousness and convulsions. Acid base balance may be important, but the evidence for it at present is based on a few observations on the blood of epileptics before attacks where there was a change toward the alkaline side, on the analogy with tetany, and on the occasional precipitation of seizures in epileptics by hyperventilation.

The inheritance of epilepsy is too much emphasized by physicians. Although the evidence supporting my opinion is far from complete, I believe that most convulsions are associated with acquired abnormality of the nervous system<sup>3</sup> and the acquired character cannot be inherited. On the other hand an injury to the brain may precipitate, and cause to become overt, a latent hereditary tendency to convulsions. The evidence for this is the observation that among the relatives of "traumatic epileptics" the incidence of epilepsy is about six times as high as among the general population, although it is only 60 per cent of the incidence among relatives of "idiopathic epileptics."<sup>4</sup>

In the list (Fig 179) trauma and birth injury (causing fibrosis, gliosis, porencephaly, etc.), meningitis, encephalitis, and tumor, are the more important clinical causes. Only six (marked +) of the causes listed are known to be inheritable,

and these, except for cerebral aplasia<sup>5</sup> are rare. Hardly ever is epilepsy inherited as a syndrome without the inheritance of other associated neurological disorders. For example, feeble-mindedness due to lack of cerebral development may be found to run in a family. That the patients also have fits is explained by the aplasia and neurological short circuiting, it is an associated symptom. Yet because the fit is dramatic the whole picture is called "epilepsy." Other inherited nervous diseases that may be accompanied by fits are tuberous sclerosis, Friedrich's ataxia, and cerebromacular degeneration. But these are so rare as to be numerically unimportant. On the whole probably less than 8 per cent of epileptics show an inherited factor as judged by a history of epilepsy in a relative. Epileptic individuals who do have epileptic close relatives should be advised against having children. The remaining 92 per cent cannot reasonably be advised against marriage (if they can find mates). More epileptics come from families burdened with migraine than from epileptic ancestors, and the taint is often carried latent in a "normal" person. Therefore, the idea of effectively eliminating epilepsy by sterilization and "eugenics" is preposterous<sup>6,7</sup>. Given laboratory control and thousands of generations it could be done.

Epilepsy means merely "seizure," a vague term at best, but it is usually understood to signify *sudden, recurrent changes in consciousness, often preceded by a sensory warning (aura) and often followed by motor discharge through the muscles (convulsion)*. Penfield and Gage<sup>8</sup> in an admirable paper on "Cerebral Localization of Epileptic Manifestations" say that under the heading of fits may be listed (besides convulsions) paresthesia, hallucinations of sight, visceral sensations, and autonomic phenomena. The list is so broad that there can be nothing typical about an epileptic fit, the essential being that *it is a disturbance of consciousness, overwhelms the victim suddenly and usually recurs in any one victim in a rather stereotyped pattern, or patterns*. In other words, each epileptic patient is likely to have his own special form of fit and to repeat it. He may have two or three which alternate, for example, it is common to have major seizures (grand mal) of one type interspersed with more frequent minor seizures (petit mal) perhaps resembling only the aura of the grand mal.

Thus it is difficult to differentiate epilepsy from other recurrent symptoms such as fainting (syncope), migraine (sick headache) and myoclonia. Syncope is often accompanied by a few convulsive jerks, migraine may have an aura and may begin entirely in the sensory sphere, but may change over into motor manifestations that anyone would call "epileptic." Moreover, fibrillary contractions, tremor, myoclonia, chorea, athetosis and convulsion form a series of muscular expressions of central nervous disorder that cannot be arbitrarily divided into those that are "seizures" and those that are not. One can talk of an attack, spell or fit of any one of them. But one talks of *epilepsy* only when there are *recurrent, rather similar attacks of disturbance of consciousness*.

Fits of a rudimentary sort may be elicited in the spinal cord, syncope and vasovagal attacks may be bulbar in origin, the diencephalon may discharge explosively giving rise to vasomotor, sudomotor and cardiac symptoms, and the forebrain with its many subdivisions gives rise to various sorts of seizures. Most attention has been directed to the cerebral cortex as the locus from which epilepsy usually arises. The conception is that a lesion in or near gray matter makes this gray matter more irritable than normal, lowers its threshold so that sudden, or slowly built up stimuli may cause a violent, disorderly neuronal discharge that we call a fit. The lesions may sometimes be actively irritating, as in the case of bleeding vessels, acute infections, growing tumors, or contracting scars. More often the lesion is more static, and seems by its mere contiguity to reduce the threshold of irritability of the adjacent gray matter, e. g., old areas of fibrosis and gliosis following injury, slowly growing tumors, cysts of softening, and arachnoiditis. In the cerebral cortex this conception seems to hold true, much evidence has been accumulated by neurologists, surgeons and pathologists that focal lesions act as the starting point from which unbridled impulses spread to cause fits. They can only cause fits if they spread into comparatively normal tissue, for the neuronal discharge must be an exaggerated and explosive one that could not come from a badly damaged nerve cell. The wild impulses are excessive and disorganized, but in causing seizures they are probably acting through comparatively normal tissue.<sup>17</sup>

The evidence for this is extensive and well substantiated by operations on the brains of conscious patients. In the first place careful clinical histories have been compared with operative findings. Still more interesting are the results of electrical stimulation of the exposed brain in conscious patients. In normal animals convulsions may be brought on by excessive electrical stimulation of certain parts of the cerebral cortex, beyond the point of physiological response. Exploring the human cortex with an electrode at operation has located not only the motor area, where special movements are represented in the precentral gyrus, but areas from which synergic movements of the opposite side may be elicited, and movements of the head and eyes toward the opposite side. This particular movement has been elicited from several locations: area 6a in the frontal lobe, near the periphery of the occipital cortex, near the superior temporal, marginal and superior parietal gyri. It is interesting that this coordinated movement of the head and eyes turning to the side opposite the lesion is probably the commonest type of onset of a convulsion. Such movements may be precipitated by electrical stimulation of the cerebral cortex of an epileptic patient, and may lead to a spread of the motor spasm to other muscle groups with unconsciousness and general convulsion, just as in a spontaneous seizure. In fact, exploratory electrical stimulation may locate low-threshold "trigger points" at which the patient's typical attack may be set off.

When such a point is near the motor area (precentral gyrus or central sulcus) the attack begins *without aura*, the appropriate muscle group begins to twitch convulsively and then the convulsion spreads in an orderly way to other muscles. This *march* is observed by the patient and he *does not lose consciousness* until fairly late in the attack if at all. When the trigger point is in the postcentral (sensory areas) the attack usually begins with a localized numbness or tingling in a hand or foot, this spreads and focal motor phenomena appear usually simultaneously in both arm and leg, with less of the element of progressive march. In the occipital area the warning for the attack may be crude *lights*, red, blue or white followed by loss of consciousness and *general convulsion*. In the parieto-occipital region the lights may be flashing or mov-

ing, causing giddiness and even nystagmus, followed by unconsciousness and general convulsion. From lesions in the temporal gyri the general convulsion is often preceded by noises, hyperacusis, tinnitus or even music, which may be accompanied by vertigo or hallucinations of unpleasant odors. Tumors near the uncinate gyrus commonly cause an aura of bad smells or taste with automatic smacking movements of the lips before the convulsion. Thus much physiological knowledge has been corroborated on the human by surgeons using the electrode and by Nature using local lesions.

Lesions of the frontal lobe are particularly interesting. Since this is the largest association area of the brain without any receiving stations for special senses (as in the parietal, temporal and occipital lobes) one would expect little or no aura. This is the case: the patient usually begins his attack with a blank stare, losing consciousness at once, but not losing motor control, for he may then perform complex movements, walk about doing aimless things and mumbling. In more sudden attacks he may turn his head to the side away from the lesion, and then turn his whole body, even spinning around two or three times before falling in a general convulsion.

All this about cortical epilepsy, however, is rather special. It is particularly interesting because of its localizing value and because patients with cortical lesions are most open to surgical help. But the recent work of Gibbs and Gibbs<sup>9</sup> shows that (in cats) the deeper structures where the rhinencephalon lies over the diencephalon give convulsions in response to electrical stimuli more easily than even the motor area of the cortex. It is as if certain tracts and cells here would set off a convulsive mechanism with greater ease than others. The fact that deep temporal lobe tumors are especially likely to be associated with convulsions is of interest in this connection. But the search for a "convulsive center" is illusory. There can be no "center" for disorganization or disintegration. Probably, because of special connections, easily traveled paths, or ease of conduction in certain areas, an electrode placed in such loci will more easily cause the unbridled activity we call a convulsion, than an electrode placed elsewhere. We know that stimulation of less organized brains is more likely to cause convulsions than stimulation of thoroughly organized ones, e. g., the convul

sions of childhood,<sup>10</sup> and there are experiments showing that after injury the threshold for convulsions is lowered<sup>11</sup> Myelization is quite incomplete in the human before the fourth year and convulsions can be easily precipitated in these years by almost any foreign element of excessive stimulation This is perhaps because of less than normal spread, *i e*, *short-circuiting* In chronic encephalitis, or postencephalitic states, there may be gliosis of the brain and the formation of connective tissue scars, cerebral hemorrhage and trauma may act in much the same way, and also the chronic degenerative diseases It may be that reduction of the number of available association pathways for nerve impulses to travel is the important factor in all these extensive lesions This, theoretically, could cause a "short-circuiting" of afferent stimuli making them discharge over efferent tracts without the normal delay caused by spreading through the wide association areas of the cortex<sup>12</sup> Such short-circuited discharge might well be explosive and disorderly and cause seizures of various sorts Other chronic processes, such as arteriosclerosis, senile degeneration, chronic arachnoiditis and porencephalic cysts, may also cause seizures by tissue destruction and this "short-circuiting" mechanism Tumors and cysts obviously cause increased intracranial pressure and damage to the tissue, but the fact that tumors of the hindbrain rarely if ever cause convulsions<sup>13</sup> and that convulsions are most common when the motor cortex is involved, indicate that there is direct irritation of motor nerve cells It might be that these tumors interfere with circulation and cause local stasis with edema, anoxemia and softening, but such changes would cause death of nerve cells and the convulsive symptoms would soon cease, clinical experience shows that convulsions caused by tumors impinging on the motor area may occur over periods of several years

It is probable that vasomotor abnormality in the brain as a primary cause of seizure has been overemphasized by some authors<sup>14</sup>, but that changes in cerebral blood flow may precipitate convulsions, is indisputable There are six conditions on the list that obviously work through anoxemia of the brain All of these six cause widespread anoxemia and convulsions The first is Stokes-Adams syndrome in which, as reported by Mackenzie, if the heart block lasted for ten sec-

onds only, unconsciousness alone occurred, but if it lasted for seventeen seconds, there was also convulsion. The onset of paroxysmal tachycardia may also be attended by seizures. Pressure on the carotid sinus with the sharp fall in blood pressure may precipitate a convulsion, but sometimes the convulsion occurs without the fall in general blood pressure.<sup>15</sup> The other two mechanisms that can be relied on regularly to produce convulsions are carbon monoxide poisoning and mechanical asphyxia, as in strangulation. In experimental animals it is always possible to produce convulsions by ligating the arteries that supply the brain, and also by limiting the oxygen that is inhaled. In patients having very frequent petit mal, Lennox<sup>16a</sup> has shown that seizures can be induced by a degree of oxygen lack that will not affect normal persons, and also by an impending induced syncope. It is obvious, however, that these conditions that cause general cerebral anoxemia are not the ordinary causes of seizures as seen in epileptic patients. Gibbs and Lennox<sup>16</sup> have shown that no *general* change in cerebral blood flow occurs before a fit. On the other hand, *local* areas of cerebral anemia may set off the neurological mechanism that causes fits<sup>17</sup> and there is good histological evidence that many convulsions, including puerperal eclampsia, are due to vascular spasm in the brain.<sup>18</sup> Some cases of Raynaud's disease and of angioneurotic edema are accompanied by seizures.

The effect of emotion and environmental stress upon epilepsy has long been recognized. Increased emotional stimuli<sup>19</sup> especially if repressed, usually increase the number of attacks. Special situations may act as conditioned stimuli and set off fits that thus are practically conditioned reflexes.<sup>20</sup> Examples of this are common in practice and patients showing possible psychological factors should be studied intensively. For example, a young woman of twenty-one was referred to me in 1932. At the age of nine she had cranial trauma and two months later onset of convulsions. She has seen many doctors and had many treatments. A régime of high enemas at twelve did no good, a nine months' trial of dehydration at eighteen made her worse, "lutein" has helped her irregular menses, but has not affected her fits, luminal helped, but has been used excessively. Because the attacks began in the left leg and



because slight but distinct neurological abnormalities were noted on the left side, Dr Wilder Penfield operated upon her at the age of nineteen and found adhesions over the right frontal lobe, excessive vascularity of the cortex and unstable arteries. These were actually observed in vascular spasm with concomitant anemia of the lower part of the motor cortex and convulsion especially in the left face<sup>21</sup>. Removal of the "trigger point" in the cortex, where a weak faradic current precipitated a convulsion (right superior frontal convolution) caused temporary hemiparesis, but eventual diminution in number and severity of the attacks. Eighteen months later she went through a severe emotional experience, thereafter there were more "minor seizures", many of these were probably anxiety states as no clouding of consciousness was observed. The emotional element was great. Since the age of ten she had been supervised meticulously, her varied and prolonged treatments had given her the "invalid habit," she was full of self-pity, said she was "utterly lonely" and could not mix with other girls or boys of her own age. She had had no regular schooling and could get no job.

To evaluate all the factors mentioned in this complex picture is difficult, but important, if one is to help this girl who is not only epileptic but hypochondriacal, psychoneurotic and drugged with luminal, coffee and cigarettes. Charting the factors helps a great deal to make the problem concrete (Fig 180). This is a "life-chart" drawn to indicate the dynamic factors in the patient's history. Each arrow represents one of the factors in the etiology of the present problem, *i e*, the fit. The lines suggest by their weight the severity of the abnormality and by their length the duration. Obviously all the factors contributing to the "nervous load" are not equally important from an etiological standpoint, but by looking at the whole chart one gets an idea of the interaction of the different elements. Certainly the main abnormality, represented by the heaviest arrow, is the *cerebral cortical scar* present since the age of nine, this is the principal cause of the fits, it has been treated surgically in the most scientific manner, nothing more can be done.

The arteries of the brain were observed in spasm, there are other indications of *vasomotor instability*, but the poor

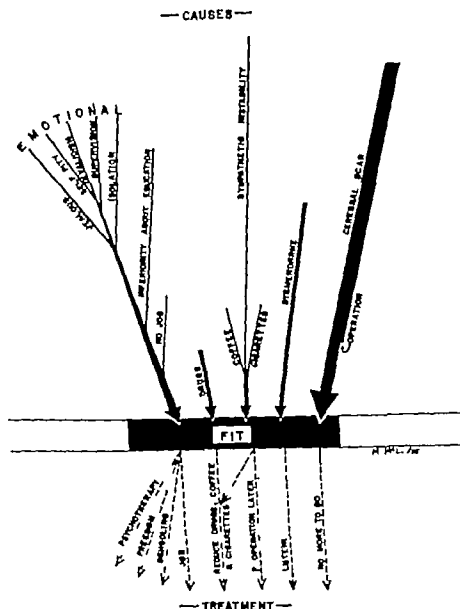


Fig 180—The diagram is drawn to bring together in the physician's and patient's minds the etiological factors in a dynamic way. Above are the various causes, indicated by arrows, converging on the patient at the time of examination. These arrows great and small make a burden too great for the patient's nervous system and a fit results. Obviously the main cause of convulsions in this case is the cerebral scar a heavy burden for many years hence represented as a long and heavy arrow. The operation improved the cerebral lesion and fits became fewer thereafter, hence the notch in the big arrow. The other arrows represent other pathological factors in the patient's life. These are individually of slight importance as compared to the cerebral lesion, but added together they constitute an important problem and probably act as the precipitating cause of many attacks. Below is shown what was done for treatment of each pathological cause. For the cerebral scar nothing more can be done. For the dysmenorrhea lutein was given. To counteract her vasomotor instability she was made to cut down on coffee, cigarettes and drugs (a sympathectomy might possibly be considered later). To improve her emotional instability she is taken away from anxious supervision given a job schooling and some psychotherapy. These are adjuncts to the surgical therapy but they make this difference to the girl she stops being an invalid lives a practically normal life is happy and has fewer fits.

general hygiene of the patient may be responsible for this, especially the excessive coffee and cigarettes. An operation to denervate the cerebral arteries by sympathectomy was considered, but it was deemed unwise to operate again upon her. General hygiene, physical training, reducing coffee and cigarettes, all have helped the vasomotor instability.

*Luminal* has been used for several years, for the last two years 3 grains per day had been given. She has been rather depressed and dozey from this and her eyes have often looked sleepy. This medicine was discontinued for a period of observation, during which general hygiene, both mental and physical, was emphasized. There was no increase in the number of seizures. *Lutein* has been found to help her painful and irregular menses, this has been continued.

The *emotional factors* are numerous. Taken singly they do not seem important, added together, however, they make a burden of anxiety, unhappiness and self-pity that is devastating, the patient was having no satisfaction out of life. It is here that one feels most hopeful about therapy. The patient needed schooling and training to give her self-confidence, she was taken from home and put under less fearful and more objective supervision. This resulted in a new feeling of freedom. A job was arranged for her part time. Psychotherapy was tried and gave her insight into what was being done for her, but otherwise it had little effect and was soon discontinued. It was the environmental treatment that helped most. During the past two years she has had only two attacks.

When such a "new deal" can be arranged for a patient, there is reason for optimism regarding the prognosis even in cases of "traumatic epilepsy." The fact that one has a scar in one's brain does not make convulsions a certain result. It is a case of summation of nervous load. When many of the factors indicated by the arrows impinge on the patient's nervous system at once, a seizure results. It is a case of the "camel's back" and many "straws." One cannot take away the scar which is the original and biggest part of the nervous load, but if the other straws are removed, the patient may well go on for years without a seizure. Symptomatically she may be "cured." And that is all the patient cares about.

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## CLINIC OF DR G P GRABFIELD

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### THE TREATMENT OF INSOMNIA

THE treatment of insomnia is a subject which can be considered from many angles. It seems wise to limit the discussion to certain phases of the subject, in order to avoid excursions into the realm of psychiatry. Texts of internal medicine do not recognize such a condition. It must be admitted that no clear, short definition can be stated. Yet all know what is meant by the term, though from an etymological point of view it simply means lack of sleep from any cause. It may be due to pain, discomfort, dyspnea, frequency, diarrhea, itching or any symptom that forces itself upon the sensorium. However, the usual idea of insomnia as a medical problem is that of sleeplessness unconnected with somatic symptoms. If sleeplessness is due to some definite cause, such as one of those enumerated above, treatment is necessarily directed to the relief of the underlying symptom. True insomnia, therefore, we may define as sleeplessness due to no underlying stimulation preventing sleep or awakening the sufferer. The condition may assume different forms.

First and most common is difficulty in going to sleep, second, awakening early and inability to sleep again, third, periods of wakefulness in the middle of the night and finally, a reversal of the sleep mechanism with wakefulness at night and sleep by day. The cause of the first three types usually is habit or some emotional disturbance either acute or as a manifestation of a psychoneurosis. The last, most distressing form is almost exclusively found in cerebral arteriosclerosis and usually is accompanied by other manifestations of senility.

Since it is axiomatic that the treatment of any symptom should be directed to its cause, and since the usual cause of

insomnia is either habit or a psychoneurosis, it is obvious that treatment must be directed against these underlying conditions. Many tricks have been advised to aid the sleepless sufferer, counting sheep, voluntary relaxation, lying in one position and various other methods of autohypnosis. While such methods may be successful in breaking bad sleeping habits or even in overcoming a superficial psychoneurosis, it is poor therapy to treat psychoneuroses by suggestion alone, and in every persistent case adequate psychotherapy applied by an expert is necessary. Often reassurance as to the harmlessness of sleeplessness is sufficient to break the vicious circle of wakefulness intensified by the worry of not sleeping and the consequent effect on the following day's efficiency. Certainly lying quietly in bed is often adequate preparation for the daytime tasks even though the hours spent in actual sleep be few. It is outside the scope of this clinic to discuss further the psychotherapy of insomnia. However, in connection with the foregoing, the indications for the use of hypnotic drugs may be concisely formulated. The following four indications for the use of soporific drugs seem clear.

- 1 Where sleeplessness can be foreseen as the result of an acute situation of short duration

- 2 Where wakefulness is clearly due to an obvious cause, and the symptomatic relief will aid in the treatment

- 3 Where the cause is unclear, but relief is urgently demanded, and no danger of masking night symptoms is present

- 4 In the reversal of the sleep mechanism in cerebral arteriosclerosis

The first group includes such situations as the near relatives of a deceased person before the funeral, the first night in the hospital and others that will readily come to the reader's mind. In the second group are such cases as discomfort from any of the causes previously enumerated. Even though the cause is unclear, and no definite disturbing symptoms are present, immediate relief of the third group of sufferers will aid subsequent therapy, even if the cause be psychic. Finally, relief in the fourth group demands the utmost care in the use of drugs to change the mechanism without intensifying it by the late action of the soporifics. This brings us to a further point to be remembered in the use of hypnotic drugs.

This consideration concerns the time and duration of action of the drug exhibited in relation to the intensity, duration and period of sleeplessness. It is well known that there are three types of insomnia, the commonest being difficulty in getting to sleep. "I stay up until I am sleepy, but getting ready for bed wakes me up, and I toss for hours," says the patient. The next tells of awakening in the middle of the night and lying awake for a period invariably longer to the patient than observation by the clock would indicate. And finally, there are the patients who awaken so early in the morning that they outdo the proverbial lark. Of course, any combination of these types may exist. The drug to be used in any given situation must be such as to combat the symptom of which the patient complains. It is all too easy and, unfortunately, too common, to give patients large doses of some momentarily fashionable or advertised hypnotic, when small doses of a judiciously selected drug would provide the relief desired. If we use the above criteria we may classify the hypnotics according to the rapidity and duration of their action. In general, these two properties are parallel. It is also an advantage to reduce the list to the smallest number that will serve. All hypnotic drugs have undesirable side actions in large doses or in susceptible individuals, and there must be included in any list a sufficient variety to allow for such idiosyncrasies.

Considering first those with rapid action over a comparatively short period of time suitable for patients unable to get to sleep, we find first of all paraldehyde and chloral both of which have stood the test of time. The obvious disadvantage of paraldehyde lies in its odor on the breath the following day, but this is often more than compensated by its efficacy and above all by the practical absence of toxicity. It must be remembered, however, that the combined use of morphine and paraldehyde is highly toxic. Chloral is undoubtedly the most useful of all the hypnotics and the cheapest. Given well diluted in water it produces sleep within an hour, and in proper doses (0.3-0.6 Gm, 5-10 grains) is entirely harmless even in heart disease. There is no doubt that in toxic doses it kills by its effect on the heart, but the fear of this side action has been engendered by the large dosage that has always been



recommended up to the last few years. None the less, it is not the hypnotic of choice in heart disease, though it may be used, if for some reason the barbitals and paraldehyde are contraindicated in a given patient. For quick action of short duration two of the barbiturate series recommend themselves. Pentobarbital (1–2 grains, 60–120 mg) has proved very useful, and it may be that “evipal,” a newer one of the series with a very rapid evanescent anesthetic action, when given intravenously, will prove useful as a short duration hypnotic with prompt action, when given by mouth.

Barbital itself is still the most satisfactory drug, where more prolonged and less prompt action is desired. In all these drugs both intensity and duration of action are increased with increasing doses. If, therefore, more than 0.6 Gm (10 grains) of barbital is found necessary to produce the effect desired, another drug should be used. Comparable to barbital but of another chemical constitution is “sabromin,” considerably more expensive than barbital but with prolonged effects. Sulphonethylmethane has fallen into disuse on account of the long period before it acts and because of its prolonged stay in the body. However, these very qualities can be utilized in selected cases. It is usually effective five to seven hours after administration and is particularly useful in the second group of patients. Its action, however, is prolonged, and it may leave a certain amount of drowsiness the next day. Furthermore, repetition over a comparatively short period, even in ordinary doses, may lead to liver damage. In occasional selected cases for short periods it may be extremely useful, especially in supplementing the action of some of the shorter acting drugs. Thus the combination of barbital with sulphonethylmethane given an hour or two before bedtime may prove more satisfactory than double the dose of barbital for producing a deep sleep throughout the night. This evidence of synergism suggests that other combinations might prove equally useful. The unfortunate one between paraldehyde and morphine has been mentioned and another between chloral and alcohol is well known, even to the underworld, in the form of “knock-out drops.” Synergism between the hypnotics and antipyretics (analgetics) has been fairly well studied in some instances. This should be utilized when pain

or discomfort is associated with insomnia. While the anti-pyretic drugs of the types, acetyl salicylic acid, amidopyrine and acetphenetidine have almost no hypnotic actions, the soporifics discussed have equally little effect on pain. Yet combinations of these two groups of drugs enhances the effects of each. In this connection it is well to remember that both morphine and codeine are inefficient hypnotics as compared with the drugs discussed. Finally, on certain occasions sleep is disturbed, largely by motor restlessness, "the fidgets," not directly associated with cerebral activity. Under such circumstances phenobarbital ("luminal") and the bromides are most useful, but their effects are prolonged on a comparatively low level of intensity. Both are poor hypnotics in the strict sense of the term and produce their quieting effect by their depression of the motor side of the central nervous system, neither should be used as simple soporifics.

Care in the selection of the soporific agent in relation to the exact symptomatology will yield excellent results. Only a small number of the vast array of sleep producing drugs on the market need be in the armamentarium of the physician. Careful clinical observation of all the possibilities of a few drugs is a suitable problem for study in private practice. Laboratory research is active in this field, but it is to be hoped that careful clinical observation checking careful pharmacologic experiment will prevent the present increase by geometric progression in the numbers of hypnotic drugs varying but little from the standard and offering no real advance in therapeutic efficiency.



## CLINIC OF DR. RICHARD M SMITH

### CHILDREN'S HOSPITAL

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#### ABDOMINAL PAIN IN CHILDREN

ABDOMINAL pain is one of the most frequent conditions in children for which the physician is consulted. The pain may be acute and seen in a first severe attack or chronic and encountered after many recurring episodes of moderate and varying intensity. The first severe acute attack of pain is often an emergency in the sense that it requires an immediate decision in relation to the necessity for surgical intervention. Too great emphasis cannot be placed upon the requirement for superior surgical technic when an operation is indicated, but it is to be remembered also that a high degree of professional skill is needed to elicit and interpret correctly the history and physical findings. Despite the urgency of the situation a careful study of the patient should be made and all possible explanations for the pain should be considered. There must be the exercise of sound judgment for improper treatment, based upon an incorrect diagnosis, may result in the death of the child. When there have been repeated attacks of pain in the abdomen the emergency may be less acute but the difficulty in diagnosis even greater.

In dealing with children as contrasted with adults there are certain things which need especial consideration. The history of any illness is of great importance but it is difficult to obtain a reliable history of an illness in a child. In infants and young children the story must be obtained from a parent or nurse. One should ask simple questions which can be answered briefly—directed toward securing exact information if possible. It is easy for a lay person to give an interpretation of facts instead of the facts themselves. Sometimes a clear description of what has happened is given by the mother or nurse. Frequently, however, the account is confused by a

limited power of observation or by extreme apprehension and an exaggerated emphasis on trivial matters. One needs to consider the temperament of the person who is giving the history. Familiarity with the family is of great assistance. When the history is obtained wholly or in part from the child one must remember the limitations of the informant. Children rarely express themselves with precision. Usually they complain less than adults and often will talk very little when they are sick. Crying may be the only presenting symptom. Serious disease within the peritoneal cavity may exist without complaint of abdominal pain either because as in infants speech has not yet been acquired or as in young children the ability to localize pain has not yet been developed. Pain apparently in the abdomen may be local discomfort caused by disease elsewhere in the body. Despite the handicaps under which one works it still remains true that the history is of prime importance.

Another consideration to be constantly borne in mind in working with children is the frequency with which the pathologic condition is dependent upon some congenital anomaly. Such anomalies are not uncommon in connection with the group of diseases which are under discussion.

Pain in the abdomen may be caused by disease or disturbed function

- 1 of some part of the gastro-intestinal tract
- 2 of some other abdominal viscus or structure
- 3 in some other part of the body and the pain referred to the abdomen

I Abdominal pain caused by disease or disturbed function of some part of the gastro-intestinal tract

Congenital hypertrophic stenosis of the pylorus

Intussusception

Intestinal obstruction

Appendicitis

Ulcer of stomach or duodenum

Colitis

Spastic colon

Indigestion—"colic" in infants

**Congenital Hypertrophic Stenosis of the Pylorus—**

This is a condition the first symptoms of which appear dur-



at which operation is performed. If done early it is good, if late, the risk is greatly increased, rising directly with the time between the onset of symptoms and the operative interference. It is not desirable to try reduction of the intussusception with enemata.

**Intestinal Obstruction**—We shall consider here only those instances in which obstruction is due to mechanical causes. Adhesions dependent upon a previous inflammatory process in the abdomen or secondary to a surgical operation may produce a similar picture. There may be complete or partial atresia of almost any part of the gastro-intestinal tract or other developmental defects such as incomplete relation of the cecum. Except when complete obstruction occurs the symptoms may be absent for many months or even years, or may be intermittent in character. Vomiting is the outstanding symptom. Pain is present in greater or less degree. The stools become scanty, depending upon the degree of the obstruction. There is usually abdominal distention with visible peristalsis. Dehydration may be extreme if the vomiting is severe. Roentgen-ray examination without barium often furnishes conclusive evidence and localizes the point of obstruction.

**Appendicitis**—Appendicitis is a fairly common disease in childhood but is unusual in infants. Recurring attacks are frequent. Often the diagnosis is missed and the symptoms explained on the basis of indigestion. The striking feature of the condition as it occurs in children is the fact that a severe pathologic condition may be present with very slight symptoms and few physical signs. In over one half of the children admitted to the Children's Hospital for appendectomy the appendix had perforated when first seen (Hudson).

The etiology of appendicitis in childhood is not different from that in adults and need not be discussed in detail. It should be borne in mind, however, that true appendicular colic is not unusual in children associated with and dependent upon an inflammatory condition in the colon.

A typical history is as follows. A child who has been previously well is nauseated and vomits perhaps once or possibly two or three times. Associated with the nausea and usually before the vomiting there may be some abdominal pain,

but frequently it is not severe or is absent and often is of short duration. Sometimes pain occurs without vomiting. Movements of the bowels may be normal. The symptoms may entirely disappear at the end of a few hours and the child appear perfectly well, but if seen at the end of this period the physical signs of appendicitis may be present. Not infrequently the attack is so mild that no physician is called and recovery takes place. It is only when a child is seen in subsequent and somewhat more severe attacks that a presumptive diagnosis in relation to the previous attacks can be made. Occasionally the pain may be very severe and vomiting may be persistent, but this history is the exception rather than the rule. On physical examination the children do not appear to be very sick. There is a slight elevation of temperature, frequently not above  $100^{\circ}$  F by rectum, or may even be normal and a moderate polymorphonuclear leukocytosis. It is possible to have a gangrenous appendix and a normal white count. Examination of the abdomen shows slight tenderness and a little spasm usually located in the right lower quadrant of the abdomen, sometimes in the right rectus muscle. True spasm, no matter how slight, should always be considered of pathologic significance. Pressure over other parts of the abdomen, especially over the left lower quadrant, may cause pain in the right lower quadrant. Rectal examination is important and frequently elicits a tender mass high up on the right just below the brim of the pelvis.

There are a number of anatomical considerations which modify materially the physical signs of appendicitis in childhood and these should be constantly borne in mind. The cecum, and therefore the appendix, is freely movable because of the long mesocecum. As a result, the appendix may be located in other portions of the abdominal cavity than the right lower quadrant. It may be on the left side instead of on the right. The appendix itself is also longer than it is in the adult and this adds further to its variety of location. When the appendix extends into the pelvis, as is frequently the case, there may be no physical signs in the abdomen. The diagnosis can be made only by rectal examination. In pelvic appendicitis not only are there no physical signs in the abdomen but there is practically no abdominal pain, but there is



discomfort on voiding or on emptying the bowel. The local inflammatory process may produce diarrhea or because of the pain there may be constipation or retention of urine. The appendix, because of its additional mobility, may be situated in the right flank and outside the cecum with the cecum over it and in front. The diagnosis, under these conditions, may be confused with an acute infection of the kidney, or if the inflammatory process extends downward, tenderness may be present just above the iliac crest. The appendix may be behind the cecum and the ileum and extend inward. This is a particularly dangerous situation because of the likelihood of general peritonitis developing.

A diagnosis of appendicitis should never be made simply on the basis of a local examination of the abdomen. It is important to obtain a careful and accurate history and to make a complete physical examination.

**Ulcer of Stomach or Duodenum**—Ulcerations in the upper portion of the gastro-intestinal tract are not common in children but they do occur, and should be kept in mind in making a differential diagnosis in abdominal conditions. The vomiting of blood or blood-tinged mucus is of particular significance.

**Colitis**—Ulcerations in the colon are very common in children. They may be dependent upon infection with one of a variety of organisms of the dysentery group. Tuberculous colitis occurs in rare instances. The onset of colitis may be very sudden with high temperature, convulsions, and marked prostration. Diarrhea may be absent for several days. Vomiting may be a prominent symptom. Pain may be slight or severe. Physical examination of the abdomen may be negative. One should remember the possibility of colitis in any acutely ill child when the diagnosis of some other condition is not clearly established. A culture from the stools is necessary for confirmation of the diagnosis.

**Spastic Colon**—A spastic colon is usually associated with a history of long-standing constipation. There may be recurring attacks of abdominal pain, often with vomiting and elevation of temperature. Physical examination reveals abdominal distention of variable degree and it is usually possible to palpate the enlarged colon filled with hard fecal masses.

A barium enema, especially if observation is made on the fluoroscopic screen during the injection shows an enlarged colon. There is sometimes resistance to complete filling, particularly at the flexures, where fecal residue has accumulated. Emptying of the colon after the enema may be incomplete and the haustral markings obliterated or reduced in depth.

**Indigestion.**—Under normal circumstances the processes of digestion go forward without our conscious knowledge and without producing any uncomfortable sensations. Due to a variety of causes, however, stimuli may be sent forth from the digestive tract, which cause mild discomfort or severe pain. When one has abdominal pain from this cause we say it is due to indigestion or colic. This diagnosis is difficult to make on the basis of positive evidence and is to be accepted only after all other possible causes of the symptoms have been eliminated.

A recent medical graduate in discussing his new experiences in practice outside of the hospital said that he had not yet seen a single case of unrotated cecum but that he had encountered numerous infants with "colic," and nobody had ever told him anything about it or what to do for it.

Colic is a term used to describe a condition seen in infants, characterized by pain in the abdomen associated with the digestion of food. Infants with colic are very fussy and restless and sleep poorly. Often they cry vigorously, especially at night. They are the babies who furnish the basis for many jibes at the solicitous father who walks the floor and the opportunity for the patent medicine vendors to dispose of "soothing syrups." Colic is seen most often in infants under three months of age. It often recurs at the same hour of the day or night.

It is not always easy to find out why some babies have colic. It is dependent upon a variety of conditions. Improper food is blamed most frequently by parents, but is the important factor less often than matters of hygiene and technic of feeding. In breast-fed babies the food may be unsuitable because the mother is tired or worried or of a temperament which makes lactation difficult. The attack upon colic, under these circumstances, should be directed toward establishing a better regimen for the mother but success is not easily attained.

In the bottle-fed baby some modification in the formula may be desirable, but if the food has been properly selected in relation to essential elements and their proportions and is adequate in amount, colic from this cause is rare. Most bottle-fed babies with colic are the victims of poor management. The feedings are given irregularly, the routine of bathing and care is haphazard, and attention is given to the point of fatigue. Food is not digested well because the processes of digestion are never allowed to proceed under normal undisturbed conditions. Sometimes the technic of giving the bottle is such that air is swallowed in large quantities, or the baby has to suck so hard as to become fatigued, or some of the other many possible errors are committed. The approach to the problem of treatment should be first to go over carefully the content of the food to satisfy oneself that it is correct, then to discuss in detail the routine of the baby's life. A long process of education may be necessary to bring about the proper daily care. Sometimes before relief of the condition is accomplished it will be necessary to introduce into the home a new person to whom the entire care of the baby is entrusted and who will carry out directions accurately. A demonstration by a short period of hospitalization is often effective. As a rule, a "colicky" baby is cured at once when placed on hospital routine, even when the food remains the same as that which was given at home. Relief of distress at the time of an attack of colic is usually possible by the giving of an enema and administering a small amount of warm sodium bicarbonate solution (1 drachm to 8 ounces of water) by mouth. Heat and mild massage to the abdomen is also helpful. It hardly needs to be emphasized that colic should be diagnosed only by exclusion of other pathologic conditions. One sees an infant crying hard with legs flexed on the abdomen, without fever—the question which presents itself for an answer is why? One must be satisfied that no other condition is present before assuming that the baby has colic.

II Abdominal pain caused by disease or disturbed function in some abdominal viscus or structure other than the gastro-intestinal tract

Diseases of the urinary tract

Liver and gallbladder disease

Pancreatitis

Tumors

Tuberculosis

Infection—nontuberculous

Purpura.

Allergy

**Diseases of the Urinary Tract**—Nephritis rarely causes abdominal pain. Acute infection of the kidney, on the other hand, is one of the common conditions giving rise to this complaint. Physical examination may reveal tenderness and spasm at the costovertebral angle and often the kidney is palpable. The diagnosis of urinary tract infection is confirmed by the finding of pus in the urine. One must remember that not uncommonly the underlying pathologic lesion is a congenital anomaly which interferes with the free passage of urine at some point between the kidney and the external urinary orifice. There may or may not be an associated hydronephrosis. Careful studies with cystogram, intravenous, or retrograde pyelography are necessary to determine the exact character of the lesion and indicate the appropriate treatment, either medical or surgical.

Renal stones are quite common in children and not rare even in infants. Pain may not be a prominent symptom. Occasionally stones in the bladder occur in children.

Renal tumors may often attain a large size beyond the stage where operative removal is possible without giving rise to pain.

Perinephric abscess is rare in children.

**Liver and Gallbladder Disease**—Acute catarrhal jaundice may cause pain in the right upper quadrant of the abdomen. Gallbladder disease, with or without stones, is not common in children. Other diseases of the liver causing pain are rare. Chronic passive congestion dependent upon cardiac decompensation is often very painful.

**Pancreatitis**—Pancreatitis is very rare in children. Occasionally the pancreas is affected in epidemic parotitis (mumps).

**Tumors**—A variety of tumors within the abdominal cavity may be found in children. Some of these give pain only when they have reached a large size, causing tension upon the capsule of an organ or have metastasized to glands, particularly

the retroperitoneal glands, and cause pain by the same mechanism. An ovarian cyst, often with a pedicle which becomes twisted, may cause severe abdominal pain and present, on examination, the findings of an acute surgical abdomen.

**Tuberculosis**—Tuberculous peritonitis and adenitis are both encountered much too frequently in infants and children. Peritonitis is more common under three years of age. Obstruction is often a prominent feature. The onset may be insidious and the condition be far advanced before there are sufficient symptoms to lead the parents to consult a physician. Adenitis may also be unsuspected for a considerable time and if the glands in the right lower quadrant are involved, as is often the case, the differential diagnosis from appendicitis may be difficult and sometimes is made only at the time of operation. Except when an operation cannot safely be postponed, the tuberculin test is of great assistance in diagnosis and if the condition is of long standing the roentgen ray may disclose beginning deposition of calcium.

**Nontuberculous Infections of the Abdomen**—Peritonitis and adenitis due to organisms other than the tubercle bacillus are common in children. Thrombophlebitis of the portal vein or some of its tributaries is not rare. Most frequently these infections are associated with infection in some other part of the body, primarily of the respiratory tract, or they may be the first presenting sign of a general septicemia or as the only evident focus of infection. It is important to appreciate the significance of this association because of the influence upon treatment. Attention should be directed primarily toward the general infection. Peritonitis of this origin is better treated by conservative methods than by immediate operative interference. In adenitis the glands themselves require little consideration.

**Purpura**—Not infrequently the abdominal lesions of purpura give rise to acute abdominal pain. A careful history with the finding of other evidences of purpura must be relied upon to establish the diagnosis.

**Allergy**—Abdominal symptoms in allergic conditions are not rare. These symptoms may be the only manifestation of the disease at the time of an acute attack or even of a chronic state, but again the history, both familial and individual, to-

gether with other allergic symptoms, should serve to differentiate this form of allergy.

III. Diseases in which there is pain referred to the abdomen.

Respiratory tract infections.

Rheumatic fever.

Diabetes.

Roseola infantum.

Lead poisoning.

Spinal disease.

Intracranial disease.

**Respiratory Tract Infections.**—Mention has already been made of the abdominal complications of respiratory infection. There are also instances in which there is no specific lesion within the abdominal cavity but in which abdominal pain occurs. Pneumonia is a classical illustration. Physical examination may be confusing for there may be few or no signs in the chest but tenderness and spasm of the abdomen. Spasm of the abdominal muscles, which is caused by disease above the diaphragm, relaxes with firm steady pressure but increases if due to disease within the abdominal cavity. A roentgen ray of the chest may reveal early pulmonary congestion or, detected by percussion and auscultation.

The toxins liberated from infectious processes in the respiratory tract may act upon the muscles of the intestines producing enterospasm, or upon the gastric and intestinal secretions, causing "indigestion."

**Rheumatic Fever.**—Carditis associated with rheumatic fever may cause abdominal pain. The other signs of rheumatic fever should prevent a misinterpretation of this symptom.

**Diabetes.**—Diabetic acidosis may be accompanied by severe abdominal pain. The explanation for this symptom is not clear.

**Roseola Infantum.**—One of the important symptoms of roseola may be abdominal pain. The age of the patient, the high temperature, and the normal physical examination are of assistance in the diagnosis.

**Lead Poisoning.**—Occasionally in children lead poisoning

may cause cramplike abdominal pain associated with constipation. This is not as commonly the case as in adults.

**Spinal Diseases**—No patient with abdominal pain should fail to have a careful examination of the spine. The roentgen ray may reveal osteomyelitis or tuberculosis.

**Intracranial Disease**—Rarely children with intracranial disease or edema associated with renal disease complain of periodic abdominal pain.

With these conditions in mind, how should one approach the diagnosis in an infant or child who complains of abdominal pain or presents symptoms suggestive of disease within the peritoneal cavity? It is essential first to remember what has been said of the importance of the history. Not infrequently a correct diagnosis is dependent upon an accurate history. The age of the patient must be given consideration because of the relative frequency of congenital abnormalities in infants. A first acute attack often presents less of a problem than recurring attacks occurring over a long period of time.

The physical examination will be greatly facilitated if one can gain the confidence of the child. Time spent in accomplishing this is amply rewarded because of the difficulty of getting reliable signs in a child who is resisting examination. Much information is revealed by inspection and may be obtained while the history is being taken and one is becoming acquainted with the child. When one palpates the abdomen one should be sure to have warm clean hands. The movements should be slow and gentle. The child should be engaged in conversation if possible. Observation of the child's face will often indicate pain more definitely than replies to direct questions. One should inspect the abdomen for distention or visible peristalsis and examine for free fluid, palpable or enlarged viscera, for abnormal masses, tumors, or accumulated feces. The character of these masses is important. Tenderness or spasm, even if very slight, is of real significance. The relaxation of spasm under slow steady pressure indicates disease above the diaphragm rather than in the peritoneal cavity. Palpation of the abdomen is unsatisfactory when the bladder is full.

One should not be satisfied with the local examination, but make a complete physical examination. The lungs deserve

especial consideration. The roentgen ray may reveal early signs of pneumonia not detectable by auscultation and percussion. In examination of the heart one should look carefully for the sign of pericarditis. Search for signs of respiratory disease should include investigation of the nasal accessory sinuses and the ears. The skin may show petechiae or other indications of a general infection. Rectal examination should not be omitted but should be done after all other procedures have been completed.

Certain special examinations may be indicated and in children with a history of recurring attacks of abdominal pain should not be overlooked. The blood may show leukocytosis, abnormal cells, reduced platelets, or stippling of the erythrocytes. The urine may contain pus or blood or crystalline elements of significance. The intradermal tuberculin test is essential in the consideration of a diagnosis of tuberculosis. Intravenous and retrograde pyelography gives valuable information about kidney structure. Roentgen-ray examination of the abdomen may show renal calculi, calcified glands, intestinal obstruction or tumor, and after barium ingestion or enema abnormal condition of the stomach, intestine, or colon. The roentgen ray of the long bones may establish the presence of an excessive deposit of lead.

Not all of the possibilities to be considered in the diagnosis of the cause of abdominal pain in children have been considered but the more important diseases have been mentioned and some indication given of the technic to be followed in reaching a correct explanation of the signs and symptoms. The process is one of diagnosis by exclusion and should be subject to periodic review unless the symptoms cease under medical treatment based upon a provisional diagnosis or after corrective surgical interference.





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### THE CLINICAL SIGNIFICANCE AND TREATMENT OF VERTIGO, DIZZINESS, AND RELATED SYMPTOMS

THERE is a tendency among physicians and patients to use the term vertigo to include such symptoms as giddiness, dizziness and faintness. Hughlings Jackson<sup>1</sup> pointed out long ago, and Symonds<sup>2</sup> has more recently stressed the fact that patients do not accurately describe their sensations through the use of such loose terms. Our experience in this clinic with patients who complain of attacks which include such sensations has led us to separate these patients into two distinct groups as regards their subjective feeling.

One group of patients complains of attacks including sensations which may be classified as true vertigo. The patients are conscious of a subjective feeling that their environment is moving about them or that they are moving about their environment. These subjective movements follow an orderly pattern which in individual patients is similar in different attacks. The patient is able to describe accurately either the direction of, or the type of movement.

The other group, which is a much larger one, consists of patients whose subjective sensations are vague and difficult for them to describe accurately. These are variously described as vertigo, giddiness, dizziness, unsteadiness, dimness of vision, and a multiplicity of symptoms of which these patients probably due to their inability to find a term adequately describe their sensations. A sensation of the body or of other objects sometimes movement is not orderly or in a direction which

can describe Such sensations are best described by the terms dizziness or faintness, and belong to that syndrome which, when severe, terminates in syncope For practical purposes these subjective sensations may be looked upon as "pre-syncopal" in nature

Thus in analyzing the subjective complaints of such a patient, it is important to determine whether he suffers from true vertigo or from symptoms of a syncopal nature There are a few distinctive features which serve to differentiate these two symptom complexes in a majority of instances in addition to the patient's description of his subjective sensations The most important differential point is that vertigo is rarely, if ever, accompanied or followed by syncope or a feeling of faintness Attacks of vertigo occur as frequently when the patient is lying down as when he is upright, and the attack is not influenced by orthostatic changes On the other hand, dizziness and syncope occur when the patient is in an upright standing or sitting position, except in a few isolated instances, and are relieved by lying down Nystagmus is common with vertigo and rare with syncope Nausea and vomiting occur with syncope but more often accompany vertigo

### VERTIGO

I should like to reemphasize that the sensation of vertigo is a subjective feeling in which the patient seems to move about his environment or the environment seems to move about the patient in a definite pattern The attacks are usually identical in a given individual Depending on its severity, the attack may be accompanied by nausea, vomiting, pallor and sweating, and the patient may stagger or fall to the ground without losing consciousness The attacks appear to be self-limited as to duration and may last from a few minutes to several hours In rare instances the vertigo is almost continuous

It is probable that the mechanism of vertigo is reflex in nature and that the cerebellum plays a major rôle in the production of such a syndrome Thus, it is apparent why sensory impulses from the semicircular canals and from the eye, both closely connected reflexly to each other and to the cerebellum, should cause vertigo so frequently Less commonly, lesions of the cerebellum, of the eighth nerve, of cerebellar tracts in



should be carried out. Sedative drugs such as bromides and barbiturates, as in epilepsy, may lessen the severity and frequency of attacks. When psychic factors and fatigue play a rôle, proper corrective measures are of aid. Furstenberg, Lashmet, and Lathrop<sup>3</sup> advocate keeping such patients in a state of negative sodium balance and acidosis by means of administering 9 Gm (540 grains) ammonium chloride daily with a low sodium diet. They have reported good results in 12 cases. Dandy<sup>3</sup> and Coleman<sup>4</sup> have obtained symptomatic cures in 42 patients suffering from Ménière's syndrome by surgical section of the eighth nerve. Such an operation appears to be safe in the hands of a competent surgeon, and should be advocated for patients suffering from repeated attacks of vertigo, tinnitus and unilateral deafness in whom intracranial lesions have been ruled out and other treatment has failed.

During the actual attack of vertigo, care should be taken to prevent the patient from injuring himself by falling. An ice-bag should be placed on the affected side and sedatives administered. The head should be placed in a position most comfortable to the patient. The attacks are self-limited and the patient soon learns when relief is to be expected.

#### DIZZINESS AND SYNCOPÉ

Observations and studies in this clinic<sup>9 10 11</sup> on a large number of patients complaining of attacks of syncope and related symptoms have demonstrated that the subjective sensations which precede fainting are similar, regardless of the cause, and can be clearly differentiated from vertigo. If true vertigo can be ruled out, dizziness, faintness, and similar terms represent symptoms which precede syncope, therefore, a discussion of such symptoms necessarily includes one of syncope also. The patient's description of such presyncopal sensations varies with the severity of the symptoms, with the nearness to the state of unconsciousness, and with the duration of symptoms before unconsciousness occurs, however, all sensations have certain definite characteristics. The patients variously describe their feeling as dizziness, weakness, faintness, unsteadiness, of "things going black before the eyes," a feeling as though they were going to faint or fall asleep, and "weak-

from watching the movement of crowds or riding in trains or automobiles, unusual noises and fatigue, or emotional reactions may be precipitating factors. For many attacks no exciting cause can be ascertained. The term, pseudo-Ménière's syndrome, is used by Dandy to describe attacks of a similar nature in which deafness is not present. Most otologists feel that Ménière's syndrome results from middle or inner ear disease, but Dandy feels that it is caused rather by functional abnormality of the eighth nerve or its vestibular branch.

**Vertigo Associated with Intracranial Lesions**—Neville<sup>5</sup> and Symonds<sup>2</sup> have recently discussed the various intracranial lesions which may produce vertigo. Suffice it to say that true vertigo may result from lesions in the cerebellum, pons, cerebrum, and cerebellar tracts as well as from increased intracranial pressure. Such lesions may be in the forms of tumor, abscess, hemorrhage or thrombosis, particularly of the posterior cerebellar artery, multiple sclerosis, arteriosclerosis, and encephalitis. These lesions may be recognized by localizing manifestations other than vertigo. Cerebellopontine angle tumors, when associated with unilateral deafness and tinnitus, may closely simulate Ménière's syndrome, but the attacks are milder in nature and other cranial nerves are also involved.

**Vertigo Due to Neurosis**—Mendel<sup>6</sup> and Leidler<sup>7</sup> describe true attacks of vertigo which occur in patients having all the characteristics of a neurosis and in whom no organic cause can be found. The vertigo tends to be present constantly and is not accompanied by deafness or tinnitus. Such patients do not respond to any form of treatment.

**Other Causes of Vertigo**—Vertigo may be caused by "toxic" agents such as alcohol and may be a symptom of uremia. It is particularly prone to occur in enteric infections and gastric upsets in children.

**Treatment of Vertigo**—Treatment largely resolves itself into specific therapy of the disease causing this symptom. In acute diseases of the middle ear and labyrinth, the vertigo may disappear when the infection subsides. In chronic disease of the middle ear local treatment may be of aid, but it is not entirely satisfactory. For persistent attacks of vertigo, general measures which tend to depress or alter reflex activity

should be carried out. Sedative drugs such as bromides and barbiturates, as in epilepsy, may lessen the severity and frequency of attacks. When psychic factors and fatigue play a rôle, proper corrective measures are of aid. Furstenberg, Lashmet, and Lathrop<sup>8</sup> advocate keeping such patients in a state of negative sodium balance and acidosis by means of administering 9 Gm (540 grains) ammonium chloride daily with a low sodium diet. They have reported good results in 12 cases. Dandy<sup>3</sup> and Coleman<sup>4</sup> have obtained symptomatic cures in 42 patients suffering from Ménière's syndrome by surgical section of the eighth nerve. Such an operation appears to be safe in the hands of a competent surgeon, and should be advocated for patients suffering from repeated attacks of vertigo, tinnitus and unilateral deafness in whom intracranial lesions have been ruled out and other treatment has failed.

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ness in the stomach " There is no subjective movement of the patient or his environment in a definite pattern as is encountered in true vertigo The symptoms usually occur when the patient is sitting or standing, and are relieved by his lying down Rarely do they occur when he is in a reclining position Being an early manifestation of fainting, such dizziness is of course encountered among a great number of subjects in whom the syndrome does not progress to unconsciousness

The mechanism and cause for various types of syncopal attacks have been extensively investigated by Weiss and his coworkers in this clinic<sup>9, 10</sup> and a summary of the entire subject by Dr Weiss can be found in the current Oxford System of Medicine<sup>11</sup> I shall discuss briefly only the most important causes for such symptoms

**Vasovagal Syncope**—The commonest cause for dizziness is that associated with vasovagal syncope,<sup>12</sup> which includes ordinary fainting attacks Such attacks nearly always occur in the upright position, and are relieved by lying down During typical attacks, the heart rate is often slow and the blood pressure low The patient is pale, sweats profusely, and the skin and extremities are cold and clammy In individual instances, any of these manifestations may be absent The attack lasts from one half to two minutes and the patient usually feels well within a few minutes after recovery The cause for such syncope is probably pooling of blood in the peripheral vascular bed, particularly in the splanchnic region This causes a diminished return of the blood to the heart and results in cerebral anoxemia Such pooling occurs more easily in the upright position, due to the added hydrostatic factor, as a result of decreased "tonus" in the peripheral vascular bed As Weiss has pointed out, "this instability or loss of tonus may be a permanent constitutional characteristic, it may be the result of prolonged rest in the recumbent position, it may be caused by bacterial toxin or other chemical substances, or it may be a temporary nervous phenomenon of psychic or neurogenic origin "

Such syncope and related symptoms are frequently seen under circumstances where patients stand in one position for a varying period of time, as when soldiers stand at attention or when crowds stand in public gatherings I am told that



a supply of smelling salts can be found in many beauty parlors for patrons who develop this type of dizziness when they sit with the curling electrodes in place and the head in a fixed upright position. The vasovagal type of dizziness is frequently encountered among patients convalescing from illness when they first assume the upright position. Psychic factors play a varying rôle in initiating or accentuating this syndrome and are the precipitating cause for dizziness or syncope encountered during venepuncture and hypodermic injections, at the sight of blood, in operating room "initiates," and following fright or other emotional reactions. Vasovagal syncope appears to be accentuated by a warm, humid atmosphere.

*Treatment* consists in correcting any factors which can be shown to contribute to or predispose to such a state. If emotional factors play a rôle, proper psychotherapy should be instituted. The patients should be reassured that such symptoms do not indicate heart disease, as this belief is held by lay people in general. As a rule, subjects who faint at the sight of blood, during injections, etc., can usually overcome this fault through their own efforts. Physical exercise and physical therapy and hydrotherapy are of aid in improving the tonus of the vasomotor system. Abdominal binders in some instances, and proper breathing and postural habits may be of aid. Patients who develop symptoms while standing in one position should form the habit of frequently shifting their weight from one leg to the other. Following prolonged bed rest, elderly patients should particularly be instructed to gradually resume the upright position and warned against standing up too soon. If organic disease is present it should be corrected whenever possible. Dietary deficiencies should likewise be corrected.

The actual attack of syncope or severe dizziness should be treated by first placing the patient in a comfortable horizontal position with the head downward. The clothing should be loosened, particularly about the neck, and cold towels or ice should be applied to the forehead and face. Olfactory stimulants, such as ammonia, seem to be of aid in aborting or shortening the attacks. Massage of the legs and abdomen may be necessary. If unconsciousness is prolonged and other

measures fail, 1 cc (15 minims) of a 1 10,000 solution of epinephrine may be given intravenously

**Dizziness and Syncope of Carotid Sinus Origin.**—Abnormality of the carotid sinus mechanism has been found to be a not uncommon cause for dizziness and fainting, and detailed discussion of this syndrome by Weiss, Baker, Capps and myself can be found elsewhere<sup>9, 10, 11, 13</sup> The carotid sinus is a plexus of nerves located in the arterial wall at the bifurcation of the carotid arteries Briefly, the attacks are similar in nature to those encountered in other types of syncope In the mild attacks, dizziness occurs without actual fainting Pallor and sweating frequently accompany the attacks but may be absent The relation of the attacks to the orthostatic position is similar to that of vasovagal syncope The attacks usually last from one half to two minutes The diagnosis depends upon reproducing the spontaneous attacks by pressure and massage of the carotid sinus, which is located in the neck just below the angle of the jaw Pressure should never be exerted over both sides simultaneously The spontaneous attacks may occur without any apparent cause or they may be initiated by turning the head, pressure from masses in the neck, extreme changes in position of the head either side-wise or upward, psychic and emotional upsets, menstruation and the menopause Digitalis and dietary deficiency have been found to have a sensitizing effect on this mechanism The syndrome occurs at any age but is more commonly encountered in the higher age groups, in which instances myocardial and vascular diseases play an important rôle The symptoms may be due to cerebral anoxemia resulting from either a reflex heart block (vagal type) or a reflex depression of the blood pressure (depressor type), or from a direct central reflex in which no change in the heart rate or blood pressure occurs and the cerebral blood flow is normal (cerebral type)

*Treatment* consists first in correcting any predisposing factors Accompanying organic disease such as central nervous system syphilis, cervical adenitis, digitalis intoxication, and dietary deficiency should receive specific treatment When such symptoms occur with the menopause, glandular therapy might be of value Patients in whom emotional factors predispose to the attacks should receive adequate psychotherapy

By changing their trend of thought, by moving about, or through the use of other external stimuli such as smelling salts, pain, etc., the patients can frequently delay or abort both the spontaneous and induced attacks. The patient should be advised as regards turning the head and wearing clothes which press against the region of the carotid sinus, if such factors play a rôle in causing the attacks.

In the vagal type of syncope, where the symptoms are due to cardiac slowing or asystole, atropine by mouth in doses of 0.5 mg ( $\frac{1}{20}$  grain) four times a day or ephedrine by mouth in doses of 30 mg ( $\frac{1}{2}$  grain) three times a day will usually prevent the attacks. If the ephedrine causes nervousness or sleeplessness, the addition of 15 mg ( $\frac{1}{4}$  grain) phenobarbital to each dose will suffice to prevent such symptoms. Ephedrine in the above dosage will prevent the depressor type of attack. The cerebral type does not respond to specific drug therapy. We have had good results in 9 of 11 such patients by surgical denervation of the most sensitive carotid sinus. The indications and technic for this procedure have been recently described by us. The operation should not be advocated except following prolonged observation and after other measures have failed, and only when the symptoms are severe enough to warrant such a major procedure.

Treatment for the acute attack is similar to that for vasovagal syncope if the heart rate is slow or the blood pressure very low, 1 cc of a 1:10,000 solution of epinephrine should be administered intravenously.

**Dizziness and Syncope due to Stokes Adams Attacks of Reflex Origin.**—The vagal type of carotid sinus syncope can be classified in this group and makes up by far the largest percentage of patients having transient attacks of reflex heart block. We have reported " " other types of reflex heart block in which the reflex was initiated in the eyeball (oculovagal reflex), esophagus, pharynx, larynx and bronchi (vago-vagal reflex) and produced attacks of heart block associated with dizziness and syncope. These attacks could be reproduced by irritation of the sensitive area and could be abolished with atropine.

As with the vagal type of carotid sinus syncope, the daily administration of atropine or ephedrine in the previously men-

tioned dosage will prevent such attacks Treatment for the acute attack is similar to that for carotid sinus syncope

**Other Types of Syncope**—A comprehensive discussion of these types can be found elsewhere<sup>11</sup> The treatment of such attacks is similar to that described for vasovagal syncope

#### SUMMARY

In evaluating such symptoms as vertigo, giddiness and dizziness, it is important to determine whether they represent true vertigo or whether they represent sensations of a syncopal nature There is a clear distinction between the two groups of sensations and they represent two separate and distinct syndromes, namely, true vertigo and syncopal attacks The subjective symptoms of vertigo and those of syncope are each characteristic, regardless of the cause

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## CLINIC OF DR JACOB H SWARTZ

### BOSTON

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#### DISEASES OF THE SKIN

##### IMPETIGO CONTAGIOSA

**Definition.**—Impetigo contagiosa is a highly contagious condition of the skin caused by a streptococcus or staphylococcus or both

**Clinical Picture**—The primary lesion of impetigo is a vesicle varying in size from pinhead to the size of a quarter. Soon after the appearance of the lesion the vesicle may become pustular. It is usually situated on an inflammatory base. The lesions tend to flatten down with the formation of a crust which is usually the color of honey. The crusts last a few days, then they are thrown off and leave a red stain which fades gradually. The vesicles or pustules may remain discrete or coalesce and form various figures such as the figure of 8, etc., thus making it easily mistakable for ringworm of the skin (*tinea circinata*).

Impetigo can occur wherever there is an abrasion or may arise from insect bites, scratches, wounds, and intentional scratches due to itching. It is most commonly seen on the face and extremities although it may involve any other part of the body as well as the scalp.

**Etiology**—Impetigo is much more common in children. It is highly contagious and auto-inoculable. It is spread from the original lesion by scratching and by careless technic in caring for it. The causative agent, as already mentioned above, is either streptococcus or staphylococcus organism or both. Impetigo contagiosa may complicate scabies, pediculosis capitis, or trauma.

**Differential Diagnosis**—Impetigo involving the scalp should be differentiated from (a) seborrhea capitis, (b)

## DIFFERENTIAL DIAGNOSIS

## HAIRY REGIONS

|  | Impetigo contagiosa | Seborrhea capitis                            | Psoriasis.     | Tinea capitis. | Pemphigus      | Favus    |
|--|---------------------|--|----------------|----------------|----------------|----------|
| Primary lesion, vesicle, pustule, or bulla | Present             | Absent                                       | Absent         | Absent         | Present        | Absent   |
| Involvement of hair sheath                 | Absent.             | Absent.                                      | Absent         | Present        | Absent         | Present  |
| Honey-colored crust.                       | Present             | Absent                                       | Absent         | Absent         | Absent         | Absent   |
| Scutula.                                   | Absent              | Absent                                       | Absent.        | Absent         | Absent         | Present  |
| Alopecia.                                  | Absent              | May be present                               | Usually absent | Present.       | May be present | Present. |
| Microscopic examination for fungus         | Negative            | Presence of bottle-shaped yeastlike organism | Negative       | Positive       | Negative       | Positive |

## DIFFERENTIAL DIAGNOSIS

## NONHAIRY REGIONS

|                                    | Impetigo contagiosa        | Tinea circinata             | Bullous erythema multiforme | Pustular eczema     | Pemphigus.      |
|------------------------------------|----------------------------|-----------------------------|-----------------------------|---------------------|-----------------|
| Primary lesion                     | Vesicle, pustule, or bulla | Pinpoint vesicle or macule. | Vesicle or bulla.           | Papule and pustule. | Vesicle         |
| Honey-colored crust                | Present                    | Absent                      | Absent                      | Usually absent      | Usually absent  |
| Duration                           | Days to weeks              | Days to weeks               | Weeks                       | Months to years.    | Months to years |
| Microscopic examination for fungus | Negative.                  | Positive.                   | Negative                    | Negative            | Negative.       |
| Iris lesions                       | Absent                     | Absent                      | May be present              | Absent.             | Absent.         |
| Eosinophilia.                      | Absent                     | Absent                      | May be present              | May be present      | Present.        |
| Mouth involvement.                 | Absent                     | Absent                      | Frequently present.         | Absent              | May be present  |

psoriasis, (c) tinea capitis, (d) pemphigus, (e) favus Impetigo of the nonhairy regions should be differentiated particularly from (a) tinea circinata, (b) erythema multiforme, (c) pustular eczema, (d) pemphigus Impetigo of the bearded region should be differentiated particularly from sycosis vulgaris (See differential diagnosis charts, p 1628 )

**Treatment**—Before treating a case of impetigo make sure of the contacts, *i e*, if there are any others in the family who have the same condition, otherwise the patient will reinfect himself It is also important to make sure, if possible, whether the playmates have impetigo

In the treatment of the impetiginous lesions we use the following lotion and salve

|              |               |
|--------------|---------------|
| R̄ Zinc oxid | ℥ij           |
| Calamin      | ℥j            |
| Phenolis     | ℥ss           |
| Liquor calcs | q.s. ad ℥viij |
| M.           |               |

Sig—To be applied twice daily morning and night.

|                         |     |
|-------------------------|-----|
| R̄ Acidi salicylici     | ℥ss |
| Sulphuris praecipitatis | ℥ss |
| Petrolati               | ℥j  |
| M                       |     |

Sig—To be applied five minutes after using the lotion morning and night.

In those cases where only crusted lesions are present and in hairy regions the lotion is omitted and the ointment alone is used

We advise against forcible removal of crusts The parts involved should be washed with boric acid solution, using a separate piece of cheesecloth or cotton pad for each involved area Wherever possible the lesions should be kept covered, especially in the case of a child In the very extensive cases the use of ultraviolet rays aiming for an erythema dose in conjunction with the above-mentioned treatment is very helpful

In cases of impetigo of the face or scalp be sure to examine for pediculosis capitis If this condition is present treat as follows pour 1 pint of carbolic acid (1 20) into a pitcher and add to it 1 pint of hot water, or use 1 tablespoonful of

95 per cent carbolic acid to 1 quart of hot water, tie a towel over the patient's eyes, place the patient's head over the basin and pour the carbolic acid solution (1 40) over the hair, catch the solution in a basin and pour it back into the pitcher Repeat the process until the hair is thoroughly soaked Allow the hair to drip over the basin for a few seconds and then tie up the patient's head in a towel for one hour To remove the nits which have been killed by the carbolic acid the hair should be combed, preferably with a wired comb known as a Derbac comb

If the above method is not practicable in some instances, the following procedure may be used the application of the following ointment nightly, followed by shampoo and fine combing in the morning This is done until all evidence of nits has disappeared

|                         |     |
|-------------------------|-----|
| R Acidi salicylici      | ℥ss |
| Sulphuris praecipitatis | ℥ss |
| Petrolati               | ℥j  |
| M                       |     |

Be sure to rule out scabies as an underlying cause If present, treat it

#### IMPETIGO CONTAGIOSA OF THE NEWBORN

**Definition**—This is a highly contagious skin condition appearing within the first few days of life and is caused by a streptococcus organism

**Clinical Picture**—The primary lesion is a vesicle or bulla, varying in size and number These rupture easily, leaving bright red, moist, denuded areas The chief location is in the folds of the axillae and groins, but may occur all over the trunk This is a serious infection in the newborn

**Treatment**—If there are many areas and the body is extensively denuded, the child should be completely undressed and placed under a cradle that is heated by electric light bulbs The bullae are cautiously ruptured, being careful not to allow the serum to run down to the normal skin by using a sterile cotton ball to collect the serum Use a fresh cotton ball for each lesion This is followed with the application of the following lotion



1. Zinc and  
Ointment  
Phenol  
Liquor cres  
M.

50  
5  
10  
25 and 50

German violet (1 per cent aqueous solution) may be used in place of the above lotion.

**Precautions.**—1 Isolate the child at the first sign of a lesion.

2 Boil all equipment that is boilable. Discard and burn all other material.

3 The nurse should wear a gown when in contact with the patient. Hands should be thoroughly washed after handling patient.

4 In the case of breast-fed infants, it is advisable to pump the mother's breasts and feed the baby from a bottle.

#### ALOPECIA AREATA

**Definition.**—Alopecia areata is a disease of the scalp characterized by the presence of sharply defined patches of partial or complete baldness.

**Clinical Picture.**—The bald patches vary in size and configuration, and may be discrete or confluent. The skin is shiny and smooth, but not atrophic. Exclamation point hairs are found particularly at the advancing border. The extent of involvement varies from one small patch to involvement of practically the entire scalp area.

In adult males the condition may be present over the bearded region.

Alopecia areata may become universal involving the eyebrows, eyelashes, the axillary and pubic regions, as well as the rest of the trunk.

**Etiology.**—Cause unknown. *Theories* (1) trophoneurotic, (2) endocrine disturbance, (3) parasitic, (4) dietary.

The trophoneurotic theory is based on the fact that cases have been reported following shock, anxiety, or worry. In rare cases the patches of alopecia follow a nerve area.

The endocrine theory is based on some good results obtained with the administration of thyroid.

The parasitic theory is based upon reported epidemics in institutions.

The diet deficiency theory is based upon cases reported improved when put on a high cystine diet

Alopecia areata must be differentiated chiefly from luetic alopecia (See chart below)

|                                   | Alopecia areata | Luetic alopecia. |
|-----------------------------------|-----------------|------------------|
| Circumscribed patches of baldness | Present.        | Absent.          |
| Moth-eaten appearance             | Absent.         | Present.         |
| Exclamation point hairs           | Present         | Absent.          |
| Other manifestations of lues.     | Absent.         | Usually present. |
| Serology                          | Negative        | Positive         |

**Treatment**—1 Complete physical examination to rule out foci of infection If present it is wise to eliminate them if possible

2 Glandular therapy, thyroid or pituitary

3 Sulphur treatment—taken either internally in the form of 5 grain tablets three times a day or collodial sulphur injections Caution—watch for mucous colitis

4 High cystine diet

5 Local treatment is used with the purpose of producing local stimulation and hyperaemia

(a) Potassium permanganate, 1 per cent, painted on morning and night

(b) The following ointments may be used in place of the potassium permanganate

|                         |        |
|-------------------------|--------|
| ℞ Acidī salicylicī      |        |
| Sulphuris praecipitatus | āā ʒss |
| Petrolati               | ʒj     |
| M                       |        |

Sig—Applied nightly

|                      |       |
|----------------------|-------|
| ℞ Phenols            |       |
| Sulphuris sublimatus | āā ʒj |
| Naphtholis           | ʒss   |
| Cerae albae          | ʒiij  |
| Adipis               | ʒv    |
| M                    |       |

(c) The Kromayer lamp to the affected parts, aiming for an erythema or vesiculation, and the air cooled lamp to the

trunk, aiming for a tonic dose. The general treatment is given about twice a week, while the treatment with the Kromayer lamp is repeated when the effects of the last treatment have disappeared.

### FUNGUS DISEASES OF THE SKIN

A fungus is a vegetable parasite which, if pathogenic, can attack skin, its appendages, such as hair and nails, mucous membrane, or the viscera. In this article a discussion of its pathogenicity as far as the skin and its appendages is in place.

**Classification of Fungi.**—Only a classification which can be applied to the clinical conditions to be discussed will be attempted. A strict botanical classification is too confusing and at present not most practical.

Group I The myxomycetes

Group II Eumycetes

The fungi pathogenic to man usually belong to Group II, which may be further subdivided as follows:

1 Phycomycetes. Reproduction by zygospores. Mycelium usually nonseptate and multinucleate.

2 Basidiomycetes. Reproduction by means of basidiospores. Mycelium septate.

3 Ascomycetes. Reproduction by means of ascospores. Mycelium is septate when present.

4 Hyphomycetes (Fungi imperfecti). Reproduction is by free borne spores (conidia). Ascus body absent. Mycelium septate. Complete sexual reproduction absent or unknown.

Fungi pathogenic to man belong chiefly to groups 3 and 4. For the sake of convenience to the clinician the above two groups may be further classified as follows:

(a) Yeasts and yeastlike organisms.

1 Saccharomycetaceae (true yeasts)

2 Cryptococcus (Torula)

3 Monilia.

4 Endomyces.

5 Coccidioidaceae.

(b) Ringworm fungi (Gymnoascaceae)

1 Microsporon

lanosum

audouinii.

Achorion

quinckeianum

schönleini.

## 3 Trichophyton

Ectotrichophyton, e g, T gypsum

Megatrichophyton, e g, T rosaceum

Favotrichophyton, e g, T ochraceum,

T violaceum

Eutrichophyton,

Neoendothrix, e g, T cerebriform

Endothrix, e g, T crateriforme, T acuminatum

## 4 Epidermophyton

The organisms which cause sporotrichosis and actinomycosis belong to the Fungi imperfecti

**Diagnosis.**—In addition to the clinical characteristics laboratory data is essential for the correct diagnosis of fungus infection. The simplest method is the *direct microscopic examination* of the material suspected

**Technic**—1 Select the proper material for examination, since many negative findings are due to selecting the material in a hit or miss manner. In tinea capitis or favus select the stumps of hairs, in tinea barbae examine the hairs in pustules or nodules as well as the seropurulent material, in blastomycosis and sporotrichosis examine the fluid in the nodules and abscesses, in tinea of the glabrous skin such as tinea circinata, tinea cruris epidermomycosis of the hands or feet, the skin scales from the roofs of fresh vesicles are to be taken for examination

2 Place some of the material between two slides which can be held together by elastic bands, label and put away for cultural purposes. The remaining material is used for microscopic examination

(a) Unstained preparation place the scales on a slide and add a few drops of potassium or sodium hydroxide (30–40 per cent). Put on cover slip and heat gently. Allow it to stand for ten to fifteen minutes for clearing and then examine with microscope

(b) Stained preparation place the scale on a slide and add a few drops of 5–10 per cent of potassium hydroxide and heat slightly. Wash scale in water for two to three minutes, using a watch crystal. Put scale back on slide and add a drop of  $\frac{1}{2}$  per cent lactophenol cotton blue, put on cover glass and heat slightly. In case of thick scales or nail preparation a 1 per cent alcoholic solution of cotton blue is used and the preparation is mounted in clear lactophenol

## TINEA CAPITIS (RINGWORM OF THE SCALP)

This is a disease of the scalp caused by different species of vegetable parasites. It is a disease of childhood chiefly and is highly contagious.

**Clinical Picture**—The following are the most characteristic findings: (1) scaliness, (2) broken off hairs covered with a grayish sheath, (3) prominent hair follicles, (4) partial baldness, (5) in some instances the follicular openings stand out as large black dots.

All or part of the above findings may be noted. The patches may be discrete and scattered, varying in size, or they may coalesce to involve almost the entire scalp. Involvement of adjacent nonhairy skin may be noted, particularly when the offending organism is of the large spore variety.

**Etiology**—The condition is most common in children under puberty, although scattered reports of occurrences in adults are present. The causative agent is a vegetable parasite either of the large or small spore variety. In this part of the country the *microsporon lanosum* is the more common offending agent.

**Sources of Infection**—(1) Pet animal, (2) contact with infected child, (3) interchanging of caps, and (4) combs and brushes.

## DIFFERENTIAL DIAGNOSIS

|   | Tinea capitis. | Impetigo.         | Schorrhea capitis.                  | Favus.    | Psooriasis.           |
|---|----------------|-------------------|-------------------------------------|-----------|-----------------------|
| Broken off hairs covered with a grayish sheath. | Present.       | Absent.           | Absent.                             | Absent.   | Absent.               |
| Silvery scale.                                  | Absent.        | Absent.           | Absent.                             | Absent.   | Present.              |
| Scutula.  | Absent.        | Absent.           | Absent.                             | Present.  | Absent.               |
| Atrophy.  | Absent.        | Absent.           | Absent.                             | Present.  | Absent.               |
| Hoary-colored crusts on nonhairy regions.       | Absent.        | Present.          | Absent.                             | Absent.   | Absent.               |
| Greasy yellowish scale.                         | Absent.        | Absent.           | Present.                            | Absent.   | Absent.               |
| Age of incidence.                               | Under puberty. | Usually children. | All ages but more common in adults. | All ages. | Usually young adults. |
| Microscopic examination for fungus.             | Positive.      | Negative.         | Negative.                           | Positive. | Negative.             |

## KERION

This is a purulent type of lesion simulating a large abscess or carbuncle and most often seen in children.

**Clinical Picture**—(1) Partial alopecia, (2) inflammation, (3) edema and boggy, (4) a carbuncle-like tumor which discharges a mucoid or mucopurulent secretion

Pain may or may not be present. Microscopic examination of the secretion or the involved hairs shows the presence of a large spored ringworm. Caution: this condition must not be mistaken for boils or carbuncles, because incision may cause a spread of the disease.

**Treatment**—The disease responds well to treatment, which consists of a daily shampoo of soap and water, followed by the application of a mild fungicidal ointment such as

|                         |     |
|-------------------------|-----|
| R. Acidi salicylici     | 3ss |
| Sulphuris praecipitatus | 3ss |
| Petrolati               | 3j  |
| M                       |     |

The child should not be allowed to attend school until the condition is cured. Boilable caps must be worn. (See Tinea Capitis)

#### TINEA FAVOSA

This disease is caused by a vegetable parasite known as *Achorion schonleini* and may involve the skin, nails, or scalp, particularly the last.

**Clinical Picture**—The following characteristics are usually found in favus involving the scalp: (1) Scutula. These are yellow cup-shaped crusts which are more commonly found at the periphery of the involved areas and resemble small mushrooms. (2) Brittleness and loss of hair. (3) Atrophy and loss of hair. (4) Offensive odor which may be compared with that of the urine of mice.

**Differential Diagnosis**—See tinea capitis.

**Etiology**—This disease is caused by a vegetable parasite known as the *Achorion schonleini*. It attacks both sexes and may occur at any age.

**Modes of Transmission**—(1) Direct contact with an individual afflicted with the disease, (2) pet animal, particularly cat, (3) contaminated articles, particularly cap, brush or comb.

**Treatment of Tinea Capitis and Tinea Favosa**—Since the infection involves the hair, the logical procedure is to get

rid of the infected hairs by one of the following procedures (a) manual epilation, (b) x ray epilation, or (c) epilation with thalium acetate.

Manual epilation can be accomplished by plucking out the infected hairs by means of an epilating forceps, or by stripping the affected areas after the application of adhesive plaster. It is advisable to cut the hairs short or even shave them in order to find the exact extent of the involvement. The manual epilation should be done daily in order to be effective. The infected hairs which have been removed should be collected in a paper bag and then burned. Following the epilation an application of the following lotion should be made on two successive days and the ointment on the third day.

|            |       |
|------------|-------|
| R Phenolis |       |
| Camphorae  | ss 3j |
| Iodine     | 3j    |
| M.         |       |

|                         |        |
|-------------------------|--------|
| R Acidi salicylici      |        |
| Sulphuris praecipitatis | ss 3ss |
| Petrolati               | 3j     |
| M.                      |        |

The following ointment may be used daily instead of the above combination.

|                       |     |
|-----------------------|-----|
| R Sulphuris sublimati | 3j  |
| Phenolis              | 3j  |
| Naphtholis            | 3ss |
| Cerae albae           | 3ij |
| Adipis                | 3v  |
| M.                    |     |

*Ethyl Iodide Inhalation*—This method of treatment was originated by Swartz, Blumgart, and Altschule and is as follows: by means of a special inhalation apparatus ethyl iodide is inhaled on two successive days and omitted on the third day. The dose begins with  $1\frac{1}{2}$  cc. (3 Gm) and is increased  $\frac{1}{2}$  cc (1 Gm) per dose until 4 cc (8 Gm) is reached. The dose for children is one half of the above mentioned. (For further information see treatment of epidermophytosis)

*x Ray Epilation*—This method of treatment is risky except in the hands of experts since the margin of safety is narrow and permanent epilation may result (for technic see

McKee's book on "x-Ray Treatment of the Skin" or other standard textbooks on dermatology) Caution no irritating or stimulating ointments should be used for at least ten days prior to x-ray treatment and for two weeks after the treatment

*Thallium Acetate* —This drug is known to cause a temporary epilation but is rather dangerous in the hands of the inexperienced, as it has been known to produce fatalities Its action is chiefly on the sympathetic nervous system The dosage is 8 mg per kilogram of body weight and it is dissolved in sweetened water made up as follows 1 teaspoonful of sugar to 100 cc of water The treatment should not be repeated within three months The first signs of epilation are usually noticed two weeks after the administration of the drug The local treatment is the same as above

**Prophylaxis** —(1) If pet animal is found to be the causative agent it should be sent to an animal hospital for treatment or disposal, (2) epilated infected hairs must be collected in paper bag and burned, (3) sterilize by boiling the clippers and other utensils after using, (4) wear boilable stocking caps These should be boiled for twenty minutes after using, (5) all outside caps that have been worn should be burned, (6) the child should not be allowed to attend school until three successive negative weekly microscopic examinations have been obtained

#### TINEA BARBAE (TINEA SYCOSIS, RINGWORM OF THE BEARD)

**Definition** —This disease is an infection of the hairs in the bearded region caused by a vegetable parasite, chiefly of the large spore variety

#### DIFFERENTIAL DIAGNOSIS

|                                    | <i>Tinea barbae</i>  | <i>Sycosis vulgaris</i>      |
|------------------------------------|--|------------------------------|
| Distribution                       | Common in the mandibular and submaxillary regions, rarely on the upper lip | Beard and upper lip          |
| Primary lesion                     | Nodule with tendency to abscess formation                                  | Follicular pustule or papule |
| Microscopic examination for fungus | Positive   | Negative.                    |



**Clinical Picture**—The chief characteristics are (1) hairs that are loose and broken off, (2) partial alopecia, (3) nodular abscesses resembling kerion, (4) location is chiefly mandibular or submaxillary regions, practically never involves the upper lip. The condition is rather rare.

**Treatment.**—(1) *Epilation*—(a) Manual epilation in conjunction with local application as in tinea capitis, (b) x ray epilation (for technic refer to McKee's textbook on "x-Ray Treatment of the Skin" or Andrew's book on Dermatology), the x ray treatments have also beneficial action upon the accompanying inflammatory tissue.

(2) *Shaving Precautions*—(a) Omit shaving brush as it cannot be sterilized by boiling, (b) new blade for each shave, (c) sterilize blade holder by boiling or by keeping in alcohol overnight, (d) do not shave too close, (e) shave uninvolved areas first and leave involved areas for last. The electric shaver has been found to be less irritating than the average razor.

#### TINEA CIRCINATA

Tinea circinata is a highly contagious disease of the glabrous skin characterized by the presence of circinate erythematous lesions with a border made up of minute vesicles. The disease is more common in children.

#### DIFFERENTIAL DIAGNOSIS

|                                     | Tinea circinata. | Impetigo contagiosa. | Syphilis.                | Eczema.                               |
|-------------------------------------|------------------|----------------------|--------------------------|---------------------------------------|
| Sharply defined border.             | Present.         | May be present.      | May be present.          | Usually absent.                       |
| Circinate lesions.                  | Present.         | May be present.      | May be present.          | Usually absent.                       |
| Vesiculation at border.             | Present.         | May be present.      | Absent.                  | May be present.                       |
| Clearing center.                    | Present.         | May be present.      | May be present.          | Usually absent.                       |
| History of contagion.               | Present.         | Present.             | Present in early stages. | Absent.                               |
| Honey-colored crust.                | Absent.          | Present.             | Absent.                  | Absent except in impetiginous eczema. |
| Serology.                           | Negative.        | Negative.            | Positive.                | Negative.                             |
| Microscopic examination for fungus. | Positive.        | Negative.            | Negative.                | Negative.                             |

**Clinical Picture**—This disease presents the following characteristics (1) circinate erythematous lesions

varying in size. Some of the lesions may even resemble the figure 8 or form a circle within a circle, (2) a border consisting of minute vesicles and crusting, (3) tendency toward clearing in the center, (4) absence of atrophy or scarring, (5) usually found on the face or neck, but may be found on any part of the trunk or extremities.

**Modes of Transmission**—(1) Direct contact with individual that has the disease, (2) pet animal (cat or dog), (3) contaminated clothing, etc.

**Treatment**.—Since the condition is contagious, the child should not be allowed to attend school. Be sure to locate, if possible, the source of infection.

Locally the lesions are washed separately, using a separate piece of gauze for each area, and a fungicidal ointment such as listed below is applied morning and night. The disease responds readily to treatment.

R Acid salicylici

Sulphuris praecipitatis

Petrolati

M

aa 5ss

5j

### CRYPTOCOCCOSIS EPIDERMICA

This condition was described by Dr C J White and Dr J H Swartz in 1928. The disease affects the female sex largely, may appear at any age and last indefinitely if untreated. It usually begins on the eyelids, particularly the upper, and may spread to the flexures of the elbows, thighs and popliteal spaces. The lesions are polymorphous, chiefly macular and infiltrative, but never moist unless secondarily infected with bacteria. In the early stages the lesions have a café-au-lait color, but later may become lichenified and even pigmented. The organism found on direct microscopic examination of the scales is a budding yeast of the cryptococcus family. The chief symptom is itching, at times severe.

**Treatment**—(1) Clothes that can be washed and boiled should be worn next to the skin, (2) a superfatted soap for bathing purposes, (3) the following ointment should be applied one or two times daily to all involved parts except eyelids.

|                           |            |
|---------------------------|------------|
| R. Mercurochrome crystals | gr x       |
| Aquae                     | m xx       |
| Acidi salicylici          | 3ss        |
| Petrolati                 |            |
| Lanolini aa               | q.s. ad 3j |
| M.                        |            |

(4) In some cases fractional doses of x-ray is helpful. The following ointment is advised in conjunction with the x-ray treatment

|              |        |
|--------------|--------|
| R. Mentholae | gr 1-4 |
| Zinci oxid   | 3ss    |
| Amyli        | 3ij    |
| Petrolati    | 3j     |
| M.           |        |

(5) Ethyl iodide inhalation. This is used in the more extensive cases. (See epidermophytosis.)

#### EPIDERMOPHYTOSIS (DERMATOMYCOSIS, ECZEMA MYCOTICUM)

This condition is caused by a variety of vegetable parasites and resulting in various clinical pictures dependent upon the location. Four types are particularly known, although others have been described.

**Clinical Types**—1 The *erythematous*—more commonly found in the folds such as the groins, perineum, axillae, and under the breast in females. The lesions are usually sharply demarcated with maceration in the fold and a slightly elevated border, frequently made up of pinpoint vesicles. In long-standing cases one may also note lichenification and pigmentation, the latter is particularly present in brunettes and in those with tendency to pigment.

2 The *vesicular type* occurs chiefly on the palms, plantar aspects, and interdigital spaces. The vesicles are intradermal, resembling sago grains, and when drying up turn brownish in color. Occasionally one may even note bullae. Secondary infection with resulting pustulation is not uncommon. In addition, there is scaling, maceration, crusting and fissures. Lymphangitis and lymphadenitis may accompany this condition, especially when the infection involves the feet.

3 *Hyperkeratotic Type*—Epidermophytosis is characterized by hypertrophy in regions in which the stratum corneum is

mally abundant On the palms hyperkeratosis is relatively mild but common, on the soles it is decidedly emphasized and still more frequent The color of the lesions is usually yellow or more often a striking orange The more common locations are the inner side of the big toe, the ball of the foot and the heel Fissuring frequently accompanies this condition

4 The *macerated form* has its predilection in the webs of the fingers and of the toes, the intergluteal fold, the contact points of the penis and scrotum, and the submammary folds This form occurs particularly in association with the above described erythematous type, especially in the folds of the skin

5 The combination of any of the above four types with one type predominating is not infrequently seen

**Treatment.**—The results in the treatment of epidermophytosis at best is not most satisfactory but with the patient's cooperation and a definite understanding of the pathology by the physician, one can frequently obtain gratifying results

The following are some of the fungicidal preparations used chrysarobin, iodine, thymol, oil of cinnamon, potassium permanganate, copper sulphate, gentian violet, mercurochrome, sodium hyposulphite, sulphur, benzoic acid and salicylic acid A keratolytic agent is necessary in combination with the fungicidal preparation in order to obtain results Salicylic acid in strengths from 3 to 6 per cent is most frequently used

The following are some of the fungicidal ointments advised

|                                  |          |
|----------------------------------|----------|
| ℞ Iodine crystals                | gr v-τ   |
| KI enough to dissolve the iodine |          |
| Acidi salicylici                 | ōss      |
| Lanolini                         |          |
| Petrolati āā                     | qs ad ʒj |
| M                                |          |

The iodine and its solvent may be omitted or it may be replaced by 1 per cent thymol or 3 per cent chrysarobin

|                       |          |
|-----------------------|----------|
| ℞ Acidi salicylici    | gr xv    |
| Acidi benzoici        | gr xxv   |
| Paraffini molli       | ōij      |
| Olei cocois nuciferae | qs ad ʒj |
| M                     |          |

|                          |            |
|--------------------------|------------|
| ℞ Mercurochrome crystals | gr x-xx    |
| Aquae                    | m xx       |
| Acidi salicylici         | ℥ss        |
| Petrolati                |            |
| Lanolini ℥℥              | q.s. ad ℥j |
| M                        |            |

Particularly useful in the vesicular type

In all instances it is wise to precede the application of the ointment by a soaking of the hands or feet in warm saturated solution of boric acid or potassium permanganate,  $\frac{1}{2}\%$  to 1 per cent solution

In the severe cases the soaks and applications are made morning and night. In order to protect the bed linen the patient is advised to wear old cotton stockings on the feet (use a woman's stocking, cut out the heel and cut down the leg part to make two ties and fasten about the ankle to hold the dressing in position). The patient should also wear cotton gloves on the hands. In the milder types, the patient is told to soak the affected parts morning and night, but the ointment is applied only at night. In the morning he is to dust a powder between the toes. Boilable socks must be worn.

The following powder is useful as a prophylaxis in epidermophytosis of the feet

|                    |    |
|--------------------|----|
| ℞ Acidi salicylici | 2  |
| Acidi benzoidi     | 2  |
| Talc               | 30 |

Caution—beware overstimulating and strong applications in the acute stages. It will only serve to aggravate and spread the condition.

**Treatment of Shoes**—Soak paper towels in formalin, being careful to protect the hands, stuff the soaked papers into the shoes and slippers. Place in a large paper bag, tie with a string and put into the closet for twelve hours. Remove the paper and place the shoes and slippers out in the sun for at least twenty four hours to air before wearing them.

**Ethyl Iodide Inhalations**—In the acute vesicular cases, in the cases with an accompanying epidermophytide or trichophytide, and in stubborn cases of long standing, the administration of ethyl iodide by means of inhalation is advised.

**Technic**—The inhaler devised by Swartz, Blumgart, and

Altschule is used This inhaler is so devised that a comfortable mixture of ethyl iodide and air is inhaled by the patient Dosage begin with  $1\frac{1}{2}$  cc (3 Gm) of ethyl iodide and increase  $\frac{1}{2}$  cc (1 Gm) per dose until a total of 4 cc (8 Gm) is reached Continue with 4 cc Inhalations are given on two successive days and omitted on the third day until marked improvement is noted, when the treatment is administered less and less frequently

Caution (1) Do not administer ethyl iodide to patients suffering from pulmonary tuberculosis or nephritis, (2) watch for an iodide rash If present, omit treatment till eruption disappears and then start gradually, (3) watch for peripheral neuritis This is a rare complication If noted, omit treatment and do not attempt inhalations again

**Prophylaxis** —The rules to be observed are (1) Do not walk around with bare feet, (2) do not wear anyone's slippers or shoes, (3) wear rubber slippers or place a towel on the shower-bath floor, (4) wash feet at least once a day with soap and water Dry thoroughly but gently, (5) apply powder mentioned in the discussion of treatment, (6) treat shoes as advised in discussion of treatment if there is any question of contamination

The treatment with trichophytin injections has not proved most successful in the author's hands However, the development of autogenous vaccines might prove to be valuable

#### EPIDERMOPHYTIDE OR TRICHOPHYTIDE

In addition to the direct infection one may see a toxic or allergic eruption which is symmetrical and which is commonly seen on the extremities, particularly the upper, and may be macular, papular, or vesicular in character It may also be follicular, lichenified, or squamous On microscopic examination one never finds the fungus in the skin scrapings from these lesions

#### EROSIO INTERDIGITALIS

This condition is more frequently seen in housewives and dishwashers It is caused by a yeastlike organism belonging to the monilia family The infection usually attacks the cleft of the middle and ring fingers or that of the middle and fore-

fingers of one or both hands, sometimes, though not often, two interspaces of one hand may be involved. The affected area is dirty white, soft from edema, sharply defined, and the border is frequently red and angry.

**Treatment.**—1 Hands must be protected from the dish water either by wearing white cotton gloves and thin rubber gloves over them or by washing dishes in such a way as to avoid getting the dish water on the hands.

## 2. Local treatment

|                           |            |
|---------------------------|------------|
| R. Mercurochrome crystals | gr x       |
| Aquae                     | ℥ xx       |
| Acid. salicylic           | 3ss        |
| Petrolati                 |            |
| Lanolin 33                |            |
| M.                        | q.s. ad 3j |

S.G.—To be applied morning and night

Cleanse the involved areas with a saturated solution of boric acid

|                           |               |
|---------------------------|---------------|
| R. Mild mercurous chlorid | gr xxx        |
| Lime water                | q.s. ad 3viij |
| M.                        |               |

Apply with gauze moistened in this solution and allow it to stay in each involved area for five to ten minutes. Do this about three times daily.

Between the applications a drying antiseptic powder should be dusted on frequently.

## TINEA VERSICOLOR

**Definition.**—An eruption of the skin involving particularly the upper trunk and caused by a vegetable parasite known as the *microsporon furfur*.

**Clinical Picture**—The lesions are macular in type, varying in size from pinhead to large patches when coalescence takes place. The color varies from the most delicate buff to a reddish deep brown, or even blackish hue. The macules are covered with a furfuraceous scale which on direct microscopic examination reveals the presence of spores and hyphae. The upper trunk is chiefly involved but it may extend to axillae, abdomen, and groins.

**Etiology**—The disease is caused by a vegetable parasite known as the *microsporon furfur* and first described by Eichstedt in 1846. It is not easily transmitted but members of one family have been known to communicate the disease occasionally to one another. This organism which is so easily

demonstrated on direct microscopic examination of the skin scales has not been successfully cultivated

**Treatment**—1 Daily hot bath followed by the application of sodium hyposulphite (25 per cent solution) or the following ointment

R Acid salicylic

Sulphuris praecipitatis

Petrolati

M

āā 3ss

3j

## 2 Ultraviolet light aiming for erythema doses

No matter what type of treatment is used, care must be taken to boil the underclothing or wash and press with a hot iron

## BLASTOMYCOSIS

Blastomycosis may be either primary or secondary to some deeper infection of the viscera or bony structure Only primary blastomycosis will be discussed here

**Clinical Picture**—Cutaneous blastomycosis is known to produce granulomatous lesions which progress slowly and are warty in character and show multiple discharging sinuses The lesions are often multiple and are most frequently seen on exposed parts, although they may occur on any part of the integument The lesions when present on the hands and feet show a greater tendency to papillomatous formation The lesions are usually covered with a thick dirty gray or brown crust which, on removal, shows exuberant granulations covered with seropurulent exudate The discharge is found to come from multiple sinuses which communicate with multiple subcutaneous abscesses The lesions show a tendency to central involution with scar formation Frequently the lesions simulate tuberculosis verrucosa cutis and can only be differentiated from it by histological and mycological studies

**Etiology**—The family of organisms causing blastomycosis belong in the yeastlike family and fungi imperfecti The belief that one individual organism is responsible for all cases of blastomycosis is not accepted by most mycologists It is generally accepted that there are a plurality of species of the fungi causing this disease

**Treatment**—(1) Surgery or surgical diathermy, (2)



x ray treatment, (3) massive doses of iodides by mouth, intravenously, or by inhalation of ethyl iodide, (4) a combination of any or all of the above methods

### SPOROTRICHOSIS

**Definition**—Sporotrichosis of the skin is a subacute or chronic infectious disease due to one of several species of vegetable parasites of the genus *sporotrichum* and characterized by the presence of subcutaneous nodules which tend to follow lymphatic distribution. This variety is the most common in America. Other varieties have been described, but because of the rarity, will not be considered here.

**Clinical Picture of Lymphangitic Sporotrichosis**—The primary sore which is a nodule or ulcer usually follows trauma and appears at the point of inoculation. The lesions that follow are multiple subcutaneous painless nodules which soften and break down. An ascending lymphangitis may accompany the nodules. This is characterized by a painless, cordlike thickening of the lymphatic vessels.

**Treatment**—Iodine is the drug of choice given orally, intravenously or by inhalation (ethyl iodide). Some recommend x ray therapy either alone or in conjunction with iodides. Iodine ointment to the lesions is helpful. Surgery is contraindicated.

### CHRONIC PARONYCHIA

**Definition**.—Chronic paronychia is an infection of the nail and surrounding soft tissue caused by a pathogenic yeast, usually a monilia.

**Clinical Picture**—The outstanding characteristics are (1) A thickening and inflammation of the soft tissue about the nail, (2) grooving and partial destruction of the nail, particularly at the lateral border and at the base. Any nail may be involved. In association with this condition one frequently finds an *erosio interdigitalis* (described above). Both conditions are found particularly in domestic servants, housewives, and dish washers. The starting point is probably trauma from the excessive use of warm water. This is later followed by a superimposed yeast infection from contact with fruits, vegetables and dish water. The cocci may produce a

picture simulating the one just described, and might necessitate laboratory studies to differentiate

**Treatment** —(Same as for Erosio Interdigitalis)

### ONYCHOMYCOSIS (TINEA UNGUIUM, RINGWORM OF THE NAIL)

**Definition** —Onychomycosis is an infection of the nail caused by a vegetable parasite

**Clinical Picture** —The involved nail is brittle, discolored yellowish brown or darker, lusterless and hypertrophic. One or all of the nails of the hands and feet may be involved. It may accompany fungus infection of the skin or it may be the sole finding. The nail bed and the lateral aspects of the finger nails are chiefly involved. Beneath the involved parts, particularly the lateral margins, are accumulations of soft débris. Involvement of the soft tissue about the nails may or may not be present. The condition is rather persistent and resistant to treatment.

### DIFFERENTIAL DIAGNOSIS

|   | Onycho-<br>mycosis | Lues            | Psoriasis.       | Dystrophy        |
|---|--------------------|-----------------|------------------|------------------|
| Pitting and stippling                         | Absent             | Absent          | Present          | Absent           |
| Yellowish brown discoloration                 | Present            | Absent          | May be present.  | Absent.          |
| Other psoriatic lesions                       | Absent.            | Absent          | Usually present. | Absent.          |
| Other manifestations of lues                  | Absent             | Usually present | Absent           | Absent           |
| Other manifestations of trophic disturbances. | Absent             | Absent.         | Absent.          | Usually present. |
| Serology                                      | Negative           | Positive        | Negative.        | Negative         |
| Microscopic examination for fungus.           | Positive           | Negative        | Negative         | Negative         |

**Treatment** —(1) *Local Treatment* —(a) Warm boric acid solution soaks for fifteen minutes twice daily, (b) scrape the involved nails with the rough side of a broken slide or with a knife until it hurts, (c) apply one of the following ointments

R<sub>x</sub> Acid<sub>i</sub> salicylic<sub>i</sub>  
 Acid<sub>i</sub> benzoic<sub>i</sub>  
 Adipis  
 M

℥ss  
 ℥j  
 ℥j

|                          |           |
|--------------------------|-----------|
| ℞ Mercurochrome crystals |           |
| Aquae                    | gr x      |
| Acidi salicylici         | ℥ xx      |
| Lanolini                 | ℥iiss     |
| Petrolati ss             |           |
| M.                       | q.s ad ℥j |

Sodium perborate paste may be used in place of the above salves. A few drops of water are added to sodium perborate powder to make a paste. This is applied to the fingernail and nail bed and covered with a rubber finger cot and allowed to stay on overnight. It is helpful to soak the nails in a warm saturated solution of boric acid before applying the paste.

2 x Ray treatment.

3 Surgery in combination with above mentioned local treatment.

4 Ethyl iodide inhalations

#### ERYTHRASMA

This condition is not common in temperate climates but it is seen often enough to merit some consideration. It is characterized by brownish, slightly scaly, fairly demarcated superficial patches involving chiefly the axillae and groins. It is only mildly infectious, and is caused by a *Microsporon minutissimum* which can be demonstrated by direct microscopic examination of the scales.

**Treatment**—Sodium hyposulphite, 25 per cent solution, applied nightly until all signs of the condition disappear or

|                         |        |
|-------------------------|--------|
| ℞ Acidi salicylici      |        |
| Sulphuris praecipitatis |        |
| Petrolati               | ss ℥ss |
| M                       | ℥j     |

℞—Apply nightly until all signs of activity have disappeared.



1. *Phragmites australis* (Common reed)  
 2. *Scirpus americanus* (Common sedge)  
 3. *Cyperus pennisetoides* (Common spikerush)  
 4. *Eleocharis acicularis* (Needle sedge)  
 5. *Eleocharis obtusa* (Broad sedge)  
 6. *Eleocharis tenuis* (Slender sedge)  
 7. *Eleocharis palustris* (Common sedge)  
 8. *Eleocharis acicularis* (Needle sedge)  
 9. *Eleocharis obtusa* (Broad sedge)  
 10. *Eleocharis tenuis* (Slender sedge)

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*[Illegible text]*

\_\_\_\_\_

\_\_\_\_\_

[illegible]

rence of edema and ascites in association with oliguria obviously is due to a breakdown in the normal control of body fluids in their relation to serum protein, liver glycogen, and portal flow. Jaundice results from the inability of the liver to excrete bilirubin and the lack of proper fat absorption from the digestive tract is intimately associated with the inadequate supply of bile acids to the bowel. Failure of the liver to excrete foreign substances at least provides an opportunity for measuring one of the liver functions, namely, the ability of the liver to excrete dye such as bromsulphalein or rose bengal and permits us to measure liver efficiency to a certain extent. The toxemia that is so frequently present in severe liver disease may be due to a combination of many of the above factors and may be associated with such varying symptoms as drowsiness, nausea, vomiting, and purpura. Acidosis may occur either in the form of a ketosis due to starvation or because of an excessive amount of amino acids in the blood with a resulting diminution of the normal alkali reserve.

If one is to treat the symptoms enumerated above and to attempt to restore to a normal level the hepatic functions which they represent to a greater or lesser extent, one must employ certain specific measures. These are, in the order of importance, complete rest, removal of any specific poison such as alcohol, cinchophen, etc., an adequate supply of simple carbohydrate and a minimal amount of fat, moderate limitation of fluid intake, a diet that contains at least a maintenance ration of protein, transfusion as needed to combat anemia and spontaneous hemorrhage, aided by adequate amounts of iron, diuretics, and possibly alkali at times to combat an existing acidosis. The principles of such treatment have been more or less generally recognized for some years, but failure to successfully treat individual cases of severe liver disease may frequently be laid to the fact that the treatment did not include a sufficient consideration of all the above factors. It is true, however, that in the past few years cases which were given up as hopeless frequently have been successfully treated with a resulting restoration of almost normal function.

The following cases are presented in brief detail as examples of adequate and successful treatment in patients suffering from serious hepatic failure.

The first case is that of an emotionally unstable woman of thirty nine who had had no symptoms prior to five years before admission to the hospital. At the beginning of this period she began to consume gradually increasing amounts of alcohol finally taking about  $\frac{1}{2}$  pint daily. She was habitually constipated until two years before admission at which time her bowel movements became more regular and less constipated. She had had an increasing number of digestive symptoms during this period consisting of anorexia, gas, nausea and finally vomiting. These symptoms had all increased strikingly in the year preceding admission to the hospital. Eight months before admission she noticed that her clothes were apparently too tight, as if her abdomen were becoming larger. Five months later the patient's sister noticed that her eyes were becoming yellow and associated with this there was noticeable swelling of the feet without fatigue dyspnea cardiac, or urinary symptoms. There was no abdominal pain at any time. During the few weeks before admission her bowel movements had become light in color. In spite of the apparent increase in the size of her abdomen she had lost 36 pounds in the last year of her present illness. Just prior to admission she consulted a doctor who told her she had a slight elevation of temperature. The history was otherwise negative.

On admission her physical examination revealed a good deal of emaciation of her arms, face and thorax. There were spider telangiectases over the face and thorax. The veins in the epigastrium were dilated. Sclerae and skin were jaundiced. Abdomen was large with some herniation of the umbilicus and there was shifting dullness. The liver edge was easily felt about a finger breadth below the costal margin. The spleen was not palpable. There was edema of the vulva, legs and feet. There was marked hyperesthesia of the feet and general tumor of the hands. Mentally she was definitely disoriented and on admission had a temperature of 101 F.

Laboratory data on admission were as follows: urine negative except for large amount of bile stool light brown in color with no occult blood. Red count 3,520,000, hemoglobin 70 Tallqvist (?) White count 18,000. Differential not remarkable. The red cells showed slight achromia and polychromatophilia with some variation in size and shape. Hinton was negative. Icteric index 40. Quantitative van den Bergh 15 mg per 100 cc. Serum protein 5 per cent.

It was felt that the patient was suffering from hepatic insufficiency probably in the nature of a subacute yellow atrophy superimposed on an alcoholic cirrhosis. Treatment was outlined as follows: complete rest in bed avoidance of alcohol, a diet consisting of high carbohydrate, low fat, maintenance of protein. Intravenous glucose therapy was instituted and the patient was given 2000 cc. 10 per cent glucose in normal saline solution.

During the first few days in the hospital the patient was extremely irrational and had a typical Korsakoff syndrome. Mental symptoms were controlled with paraldehyde and subsided after three or four days. The jaundice definitely increased during the first three weeks, reaching a peak at this time with a quantitative van den Bergh of 25 mg per 100 cc. At the same time there was a very definite increase in the amount of abdominal fluid and the patient became rather stuporous and unable to eat except in very small amounts. Oliguria was striking during the second week of the hospital stay the patient putting out only 10 to 20 ounces of urine a day during this period. Ten days after admission she weighed 133 pounds or 10 pounds more than when she entered the hospital. Because practically all the veins were thrombosed it was necessary to discontinue the intravenous glucose therapy at this time.

On the tenth day abdominal paracentesis was performed and 3000 cc of straw-colored fluid was withdrawn, specific gravity 1011 but otherwise not remarkable. The following day 1 cc of salyrgan was given intraperitoneally without effect. A day later because of the patient's very poor condition and the fact that her anemia seemed to play an important part in her condition she was transfused with 600 cc of blood and was again transfused six days later with the same amount. Salyrgan was again administered the second day after the transfusion with a moderate diuresis but following this there was a return of oliguria and a gradual rise in temperature until it reached 103° F after five days. At this time the patient was so ill the second transfusion was performed and this was followed by a third injection of 2 cc of salyrgan without any appreciable result. Two days later, or three weeks after admission, a second abdominal paracentesis was done with withdrawal of 4300 cc of fluid of the same character as that obtained the first time. A third tap was performed five days later at which time 4000 cc of fluid were removed. Following the second paracentesis the spleen was easily felt and continued to be palpable throughout the remainder of the acute illness. Following the second transfusion the patient's appearance was distinctly improved and along with a slight drop in temperature her symptoms of anorexia, nausea, and vomiting began to subside. Coincidentally, the stools which had been clay-colored began to return to a normal color and the jaundice diminished so that four days later the van den Bergh had dropped to 20 mg per 100 cc. Improvement was gradual from this point on, the jaundice diminishing and the van den Bergh dropping to 7 mg per 100 cc one month after admission, at which time the patient was putting out a slightly greater amount of urine. A fourth and final paracentesis was performed almost five weeks after admission, at which time 4 liters of fluid were removed. On the same day 2 cc of salyrgan were given intramuscularly with a very excellent diuresis, the first that had been obtained. Eight days later a final intramuscular injection of 2 cc salyrgan was administered, this time resulting in a diuresis which lasted for three days with a loss of 4 pounds in weight. At this time the patient was practically symptom-free, was eating well and had improved mentally to such an extent that she was essentially normal.

She was discharged from the hospital seven weeks after admission with no evidence of ascites and very slight jaundice. The urine was free from bile and the stools were normal in color. The subsequent course of the case indicated that there was a very definite underlying cirrhosis which was also borne out by the finding of a positive Takata-Ara test.

This case illustrates well the various measures which can be employed successfully in a case of extreme hepatic insufficiency. The failure of liver function was evidenced by jaundice, drowsiness, nausea, vomiting, oliguria, edema, ascites and anemia. The specific measures which were employed were the administration of adequate amounts of carbohydrate by mouth and vein, relative limitation of fluids, complete rest, removal of the toxic substances that caused hepatic insufficiency, in this instance alcohol, the use of diuretics, transfusion, and subsequently, large doses of iron.

Two points are of interest. The first was that the patient



did not begin to improve until after two transfusions, which apparently brought about clinical improvement as well as an immediate rise in the red count. The other point of interest lies in the fact that a diuresis occurred at about the time when the patient's liver began to function more efficiently. In this instance it was apparently produced by the use of salyrgan, although only after the drug had been given four times. It is worthy of note that at times salyrgan therapy has to be continued for a long time before it becomes efficacious and it may well be that a certain degree of liver efficiency is necessary before a diuresis is possible. The case also illustrates the fact that acute liver failure may be superimposed upon a symptomless or nearly symptomless cirrhosis and, if properly handled, may not be inconsistent with almost complete recovery.

The patient has completely abstained from the use of alcohol and has been extremely careful in her manner of living and eating. As a result, her strength has gradually returned and one year after discharge from the hospital she is in apparently good health with no evidence of edema, ascites, or jaundice, although the liver and spleen are still easily palpable. A second case is of interest as illustrating how thorough a recovery can be made from what is apparently complete hepatic insufficiency when treated by adequate measures.

The patient was a woman forty-seven years of age, with a negative past history except for a mild attack of catarrhal jaundice at the age of twenty.

Four months prior to admission to the hospital the patient was bothered by joint pains and was treated with fairly large doses of cinchophen (farastan). At about the time that cinchophen therapy was initiated the patient had a severe upper respiratory infection which lasted for several weeks. Two months before admission she noted the onset of malaise, weakness and nausea and a week later noted jaundice, dark urine and clay color stools. She stayed in bed for a few days but was up and around for six weeks before admission with increasing loss of strength increasing jaundice and itching. For three weeks before admission there was edema of the feet and swelling of the abdomen. She had, in addition, a dry cough and a pleuritic pain at the left axilla which persisted for several weeks before admission.

Physical examination showed a deeply jaundiced fairly well-developed and nourished woman with purpuric spots over her body and excoriations from continuous scratching. There were signs of a bilateral hydrothorax and, in addition, there was obvious ascites and edema of the legs and ankles. Careful palpation showed the edge of the liver to be about 3 fingers below the costal margin and tender. The tip of the spleen was just palpable. Laboratory examinations showed a highly colored urine containing a large amount of bile

and light brown stools. The red count was 3,900,000, the white count 7000, hemoglobin 60 per cent, differential not remarkable. A bromsulphalein test showed 85 per cent retention of the dye at the end of one-half hour. A quantitative van den Bergh showed 5.5 mg bilirubin per 100 cc of blood.

Treatment was instituted promptly and consisted of absolute rest in bed, discontinuance of cinchophen, a diet containing about 450 Gm of carbohydrate a day and the intravenous administration of 1000 cc 10 per cent glucose in normal saline. The intravenous glucose was discontinued after four days because of the striking clinical improvement. A marked diuresis was obtained after the fourth day and a high urinary output was noted from this time throughout the following eighteen days. There was a corresponding loss of weight and improvement in the signs and symptoms. Within eight days there was an actual loss of 24 pounds with complete disappearance of ascites and edema. Jaundice also rapidly diminished and at the end of three weeks the quantitative van den Bergh was only 3.5 mg per 100 cc and a bromsulphalein test showed only 25 per cent dye retention at the end of an hour. At this time the liver and spleen were not palpable.

Such a rapid change in a very striking clinical picture illustrates well several facts. In the first place, the physical signs were those of almost complete liver insufficiency with jaundice, purpura and abnormal retention of water in the tissues and serous cavities. The patient was seen by several consultants and all agreed that her condition was precarious. The cause of the hepatic disturbance was obviously cinchophen, a known liver poison, and very grave concern was held regarding the prognosis. In spite of this, very simple treatment was associated with a very striking reversal of the picture, with all the signs and symptoms disappearing very rapidly. In this case the three important factors undoubtedly were rest, removal of the specific toxin, and an adequate carbohydrate intake. One point to be particularly noted was the very striking retention of fluid due to liver insufficiency with a rapid restoration of normal fluid balance once the liver cells had been restored to normal function. It is also of interest to note that the patient's recovery was complete and there had been no untoward symptoms during the past four years.

**Summary**—The preceding protocols bring out practically all the essentials of successful treatment of hepatic insufficiency. The two patients were critically ill from what amounted to subacute yellow atrophy. The various functions of the liver were restored to normal by the measures already stressed, namely, rest, removal of toxin, adequate carbohydrate intake, the use of diuretics, and abdominal paracentesis when

required, blood transfusion, and iron therapy. Rarely the use of alkali to combat an existing acidosis due to failure of deamination of amino acids is indicated, but in these two instances this was not the case. By similar measures it undoubtedly will be possible to successfully treat almost any type of liver disturbance, infectious or toxic in nature, provided surgical measures are not indicated. The essential considerations are a proper evaluation of the degree of liver insufficiency, the speed with which treatment is instituted, and the thoroughness and persistency with which the various measures are carried out.



## CLINIC OF DR FREDERICK C IRVING

BOSTON

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### PRENATAL CARE IN PRIVATE PRACTICE

I SHALL present for your consideration the case of Mrs R, a primipara of twenty-two, who came to my office on January 15. Her last menstrual period began November 5 and there has been no bleeding since this date. She has always been regular in her catamenial habits since she first began to menstruate at the age of fourteen and she has never skipped a period. The flow has always been moderate in amount, appearing every twenty-eight days, and never requiring more than four pads on any one day. She never passes clots. The duration of the period is usually five days. There is no pain either just prior to the period or during its course, and there is no interference with her daily routine of life. She was married on September 5. Neither she nor her husband have taken any contraceptive precautions, as they have both wanted children.

It is apparent that Mrs R has had a normal menstrual history and the presumption is that she is pregnant. The next step is to ascertain if she has any of the other early subjective evidences of gestation. She says that about a month after missing her first period she began to have considerable nausea on awakening and that on several occasions she has vomited her breakfast. This condition still persists. When questioned regarding the condition of her breasts, she states that they are tender and distinctly enlarged. She has to urinate more frequently during the day and must arise for this purpose once during the night, which has never been the case before. She is sleepy at times and finds herself taking naps during the afternoon.

Before proceeding to a physical examination it will be convenient at this point to go into the patient's past history

Both her parents are living and have had no serious illnesses. She is the oldest of three children. She had measles in childhood and has had her tonsils removed twice. An appendectomy without drainage was performed at fourteen. She has had no other surgical operations, nor has she broken any bones. She has never had scarlet fever, diphtheria, pneumonia, rheumatic fever or heart or kidney disease. Since the removal of her tonsils she has not been subject to sore throats or colds. Her weight has not varied much for the past two years. She plays ordinary games for pleasure but does not consider herself particularly athletic.

The patient is of medium height and weighs 120 pounds. General examination reveals nothing of interest. Her teeth are good. Examination shows the second laryngological attack upon her tonsils to have been victorious. The heart and lungs are normal. The breasts show no abnormalities, but the veins underlying the skin are prominent. The nipples project from the areolae, which contain a number of enlarged Montgomery's tubercles. The abdomen is negative, save for a linear scar about 2 inches long in the right lower quadrant. There are no herniae. The fundus of the uterus is not felt above the symphysis nor are any abdominal tumors made out.

The feet are placed in stirrups, the legs draped with a sheet. My nurse washes her hands and then prepares the vulva with cotton pledgets soaked in mild soap solution and warm water. I wash my hands and draw a dry sterile glove onto my left hand. Strict surgical asepsis is not necessary for such an examination. The labia are separated with the right hand. The mucous membrane of the introitus is slightly blue. The left forefinger, well covered with surgical lubricant, is gently introduced into the vagina, being particular to avoid the clitoris, which may be quite sensitive. I find by bimanual examination that the uterus is slightly enlarged and somewhat soft. The tissue about the external os is velvety in texture. Mrs. R., who is somewhat apprehensive, contracts her abdominal muscles so that further investigation is impeded, although she says that I have not hurt her. I therefore direct my nurse to raise the head of the table and I ask the patient to breathe deeply. These expedients have the desired effect. I am now able to introduce both my fore and middle fingers

and palpate bimanually each time the patient expires. I find that there is a distinct softening at the isthmus of the uterus, the so-called "Hegar's sign." I can feel the left ovary, which appears normal, the right I cannot make out. I reach cautiously for the promontory of the sacrum but am unable to touch it. The vaginal examination is completed by the introduction of a well lubricated vaginal speculum. The portio vaginalis is distinctly purplish, the external os is nulliparous in form, the discharge is clear mucus and normal in amount and there are no cervical polyps visible.

With the patient in the same position I palpate and measure the pelvic outlet. The symphysis is of normal height and inclination, the arch is wide, being Roman rather than Gothic in architecture. I show Mrs. R. the outlet pelvimeter, and tell her that from now on I shall take measurements only, that there will be no further internal examination and that she will not be hurt. I insert my thumbs in the rings of the pelvimeter and place them upon the ischial tuberosities. The widest measurement so obtained is the correct one. I find it to be 10 centimeters, which is quite normal, and then measure Schuman's pubotuberous diameter, which is obtained by placing one tip of the large pelvimeter upon the left ischial tuberosity and the other upon the top of the pelvic bone. This distance is 10.5 cm., which is also normal. So far I have found that the pelvis is not male or funnel in type, since the outlet is not contracted nor is its height greater than one would expect in a normal woman.

The leaf at the foot of the table is raised and the patient's legs extended upon it. The legs are covered and the abdomen exposed. I place the tips of the pelvimeter upon the widest point of separation of the iliac crest and find it to be 28 cm. I then lay them upon the most prominent portions anteriorly of the iliac crests and make this measurement 25 cm. I ask Mrs. R. to lie on her left side and to bend the left knee, while she keeps her right leg straight. I identify the spine of the last lumbar vertebra and place one branch of the pelvimeter just below it while the other rests upon the anterior surface of the symphysis. I so obtain the external conjugate, which is 20 cm.

All of Mrs. R.'s measurements of the upper pelvis are nor

mal In general it may be said that whatever are the actual measurements, the interspinous is usually 3 cm less than the intercrystal and the external conjugate 5 cm less than the interspinous When these proportions do not hold either there is gross pelvic deformity or, as is more frequently the case, the examiner is in error The distance between the trochanters of the femora is not taken, because the measurement is of no value

In spite of the information we have obtained regarding this patient's pelvis we have no real knowledge concerning the size of the interior, which is what interests us most, since the external measurements bear no close relationship to those within However, since Mrs R's long bones are normal for a woman of her height and weight, we may assume that her general skeletal development is also normal and that there is no reason to fear pelvic contraction Accurate information concerning the interior of the pelvis can be obtained only by determining the diagonal conjugate, which, in Mrs R's case, was impossible without anesthesia, or by r-ray measurements x-Ray measurements are not indicated as a routine and are only of value at the end of pregnancy if the presenting part does not enter the pelvis

I inform Mrs R that she is presumably pregnant She wishes to know if more definite information can not be obtained by performing the "rabbit test," about which one of her friends has told her The reply is that the lapse of time will give an equally accurate answer and at no expense There seems to be a tendency at present to perform the Aschheim-Zondek test in cases where an immediate diagnosis is not essential This probably results from a desire to employ so-called "methods of precision" and to avoid making a diagnosis on the basis of skill and personal experience It should be remembered that the Aschheim-Zondek test and its modifications are not invariably accurate and that false negatives have on some occasions been reported in early pregnancy

Mrs R is then instructed regarding prenatal care She is directed to come to the office every month until the last three months of her pregnancy, after which she will be expected to report every two weeks An appointment is made for her next visit and a card bearing the date and hour is



given to her for a memorandum. The nurse, who reports that the specimen voided in the office is normal, gives her a small clean bottle containing a few drops of chloroform as a preservative and enclosed in a mailing case. She is instructed to place in the bottle a mixed day and night specimen of urine, obtained by saving what she voids on going to bed, and what she passes during the night and on arising in the morning. She is also warned to place in the mailing tube a slip of paper bearing her name, since the identification of unmarked specimens is difficult, if not impossible. These specimens may be sent conveniently by mail. When they arrive at the office the color, reaction, and specific gravity are noted. The filtered urine is tested for albumin by the nitric acid method. If a suspicious ring is obtained the heat test is performed on a specimen. If albumin is found the centrifuged sediment is examined microscopically. The urine is always tested for sugar, since only in this way can the presence of latent diabetes be detected. If a reducing substance is found it may be glucose or lactose. Yeast ferments glucose but not lactose. A blood sugar determination is indicated when a positive sugar test is obtained.

It is well to follow a definite routine in instructing new patients so that nothing essential will be left out. The instructions apply to diet, care of the bowels, exercise, rest, clothing, bathing, and end with a brief recapitulation of the untoward events which should lead the patient to consult the doctor immediately.

Mrs. R. informs me that she has a considerable amount of nausea and that she occasionally vomits in the morning. She is told to eat two unsalted crackers and to drink a little water or a cup of black coffee before rising and to stay in bed half an hour thereafter. Her breakfast is to be a small one, consisting of cereal, dry toast and coffee, or a boiled egg, dry toast and coffee with orange juice. At 10 30 A. M. she has a slice of bread and butter and a glass of milk or a cup of cocoa. At 1 00 P. M. she has her luncheon, which may consist of soup or broth, a green vegetable or salad, bread, toast or rolls. At 4 30 P. M. she has tea. In addition there is toast, or bread and crackers with strained honey, jam or marmalade. At 7 00 P. M. she has a light dinner consisting of meat and vegetables.

with soup or dessert Before retiring Mrs R has a glass of milk or a cup of cocoa with bread or crackers All fats, such as cream, or an excess of butter, or olive oil in salad dressing, are avoided, also fat meats, as bacon, ham, pork, certain fishes (salmon, herring, mackerel, bluefish) No food should be fried On the other hand, carbohydrates may be given freely, including those containing sugar Lean meat has no harmful or beneficial effect

The patient is told to go about her daily activities with as little regard to her nausea as possible She is asked to report by telephone if she does not improve within a week and is told that if she still feels ill a prescription will be sent her This will consist of sodium luminal,  $\frac{3}{4}$  grain, to be taken twice or thrice daily

Mrs R says that she has always been constipated and that this condition is even more marked since she has skipped her periods The necessity of regular daily bowel movements is impressed on her She is told that green vegetables, whole wheat bread, bran, cereals, 6 to 8 glasses of water daily and the habit of using the toilet at the same time every day will do much to set things right If a laxative is needed it is administered preferably at night in pill or tablet form, as less likely to provoke nausea Mineral oil, while excellent, is more appropriate later in pregnancy, when the stomach is in a more receptive condition

Many dentists believe that the administration of calcium and vitamin D will prevent dental caries Two glasses of milk, about 500 cc, contain 0.5 Gm of calcium, which with the amount obtained in other foods should be enough for the needs of the fetus If the patient does not like milk or if the physician fears that its ingestion will produce too marked a gain in weight, calcium may be provided in the form of gluconate or a similar absorbable form Vitamin D may be given in any of the standard preparations

The patient is told to forego all forms of athletic exercises, but to take a walk every day, lasting from half an hour to one hour She is not to lift heavy objects or reach for things on high shelves or hooks which may require her standing on tiptoes She may take warm baths, but is to avoid those which are very hot or cold She is to mark off on a calendar

the days when she would be menstruating if she were not pregnant and is to avoid intercourse, undue exertion or social activities at those times. She is to take a rest every afternoon and to be in bed by 10 o'clock except when she goes out in the evening for entertainment, which should not be more than twice a week.

Her clothing should be appropriate to the season. Constriction of the waist is avoided and clothes are to be hung from the shoulders. Round garters or rolling the tops of the stockings may predispose to varicose veins. Shoes should be comfortable with moderately low flat rubber heels. If she habitually wears a girdle she may continue to use it until it becomes too tight. Later a maternity support may be required, but this depends solely upon the patient's comfort and confers no particular benefit upon the mother or child. Should it be necessary to order such a support the patient is sent to a corsetiere who will carry out the doctor's wishes. Many dealers in such garments, if not checked, will sell the patient an elaborate and expensive corset which is only of use to very large, stout women.

Mrs. R. is told that she is to report by telephone immediately and go directly to bed if she has any vaginal bleeding or abdominal pain. She is also informed that she is to consult me freely if anything occurs which she does not understand or if she wishes any advice. She is cautioned against the medical lore of her married relatives and friends. At this time also she is warned of the other danger signals of later pregnancy which are indicative of toxemia such as headaches, blurring of vision, abdominal pain and swelling of the face or extremities.

Over half an hour has been spent at the first call. Subsequent visits will require less time, as it will only be necessary to take the patient's blood pressure, weigh her and ask her certain routine questions. In early pregnancy these concern bleeding, abdominal pain, the frequency with which her bowels move, and the general state of her health. At the beginning of the second half of pregnancy one should ascertain the date of quickening and from this information calculate expected date of confinement to see if it agrees with that obtained by counting from the first day of the last period. In the event

of a marked discrepancy between the two dates, more reliance should be placed upon calculation from the last menstruation, since the first detection of fetal motions is entirely subjective and introduces an element of individual variation

If all is going well it is not only unnecessary but an annoyance to examine the patient every time she comes to the office. Any symptoms, however, should be carefully investigated. About two months before term the abdomen should be palpated to detect a possible breech presentation, since an external version may be more easily accomplished at this time than later in pregnancy. Three or four weeks before the expected date of confinement the patient is examined vaginally under strict aseptic precautions. The presenting part is identified and its station in the pelvis determined, whether it is low, mid, high or floating. One notes whether the portio vaginalis is shortened or effaced, the consistency of the cervix and how many fingertips the external os and the internal os admit. The diagnosis of position is made almost entirely by abdominal palpation. The fetal heart tones are ausculted. About this time the patient may ask if the baby is going to be a boy or a girl. The truthful physician will tell her that he does not know. If he ventures into the realm of prophecy he will be wrong half the time. A large uterus with confusing fetal landmarks, even though only one fetal heart is heard, warrants an x-ray examination to settle the question of twins. It may startle the patient and her husband as well as embarrass the doctor at the time of delivery if nature's generosity is not known beforehand.

Nothing more is heard from Mrs. R. until two weeks later, when she telephones to say that she has noticed the escape of a small amount of bright blood from the vagina, in all, less than a teaspoonful. There is no pain and she is now in bed. I tell her not to get up and that I shall see her as soon as possible. I also inform her that I shall want her to remain in bed for some time and that I shall send a nurse to her house to care for her. Since the original pelvic examination revealed no masses or abnormal tenderness it is unlikely that the bleeding indicates an ectopic pregnancy, rather are the chances in favor of a threatened abortion.

I find the patient in bed and perfectly comfortable. There

is a little fresh staining on the vulvar pad. I do not make a vaginal examination for fear of loosening further the ovum from its attachment. I cautiously palpate the lower abdomen. I feel the fundus of the uterus just at the symphysis pubis, which is commensurate with the estimated duration of pregnancy. There is no tenderness anywhere. She says she still feels slightly nauseated but that things have improved greatly. I instruct the nurse to keep Mrs. R. in bed. She is to use the bed pan instead of the toilet. She may have two pillows but is not to sit up. No attempt is made to move her bowels for twenty-four hours, when she is to have an oil enema, to be followed later by mineral oil by mouth. Most authors of text books advise the use of morphine in threatened miscarriage to diminish uterine irritability, but this therapy seems to be based on a misconception of the mechanism of miscarriage. The first step in abortion is bleeding into the spongy layer of the decidua basalis. It is not until the hemorrhage becomes of sufficient extent to distend the uterus or separate the ovum that the uterus reacts and attempts to expel the product of conception. It is therefore difficult to see what beneficial effect morphine can have in preventing the completion of an abortion, although its use is justified to relieve pain when an abortion is actually in process. The application of an ice bag to the suprapubic region can do nothing unless it is to stimulate uterine contractions, which is what we wish most to avoid.

Mrs. R. remains in bed for one week after all bleeding has stopped. The first day up she is allowed to sit in a chair, the next day, although restricted to the same floor, she may walk about and the third day she may go downstairs to dinner. Her activities are gradually expanded and the nurse is omitted. On wholly empirical grounds the patient is given a half a grain of thyroid extract daily and is encouraged to eat articles containing vitamin E, such as lettuce, corn, and wheat germ. If the attendant wishes he may attempt to increase the amount of progesterin (corpus luteum hormone) by administering a suitable glandular product, if he realizes that there is at present no convincing clinical experience to justify him in his course of treatment. Intercourse, exertion, travel and auto-mobiling are forbidden for at least a month.

For the present Mrs. R.'s pregnancy progresses normally.

At her visit of April 9 I find that she first felt the baby move on March 24. Since she is a primipara I add twenty weeks to this date and find the expected date of confinement to be August 11, which agrees well with the date of August 12 obtained by calculation from the first day of the last period. She feels very well indeed and is evincing interest in food.

On May 7 I find that Mrs. R. has gained 5 pounds since her last visit. Her urinalysis and blood pressure readings are normal. The question of diet is discussed in some detail. She has been to visit her mother, who has urged her to eat large quantities of food so that she may have a nice, large, healthy baby. Patient explanation at least partially convinces Mrs. R. that the amount of food she eats will have very little effect on the size of the baby, but will have a very considerable effect on her. She is told that an accumulation of fat will make it more difficult for her to give birth to the baby and that it may make the difference between a normal and an operative delivery. The final argument that a great increase in weight may spoil her figure appears to produce some impression. She is told to weigh herself twice a week on the same scales and not to gain more than half a pound a week. A printed diet list is given her, showing the caloric value of various foods and she is instructed to restrict her daily intake to 2000 calories. She is especially cautioned against an excess of fats, sweets and starches.

At Mrs. R.'s next visit on May 21, I find that she has attended faithfully to her diet and has only gained  $1\frac{1}{2}$  pounds in two weeks. She complains of constipation and heartburn. She is told to eat plenty of fruit, green vegetables and whole wheat bread. A suitable preparation of bran is advised for breakfast. She is instructed to cultivate regular hygienic habits and to drink an adequate amount of water, 6 to 8 glasses daily. A tablespoonful of mineral oil is prescribed half an hour before each meal and at bedtime, with instruction if the oil should escape by rectum to reduce each dose, but not the total number of doses. For the heartburn calcium carbonate is prescribed in 5 grain tablets to be carried with her and taken *ad libitum*. She is also cautioned to avoid spiced, fried or highly seasoned foods and is warned that no per-

manent improvement may be expected until after the birth of the baby

On July 16 Mrs. R. has her antepartum examination. The portio vaginalis is shortened but not completely obliterated, the external os admits a fingertip, but the internal os is closed. The lowest part of the vertex is just above the imaginary line joining the ischial spine. Abdominal palpation also shows the head to be engaged, the fetal small parts are felt in the right flank and the fetal heart is best heard on the left. The position is left occiput anterior. The uterine fundus is almost at the costal margin.

On July 30 I find that Mrs. R. has gained 6 pounds in the last two weeks. Her ankles are slightly puffy and her face is beginning to have the full appearance characteristic of edema. The blood pressure is 120/84 and the urinalysis is negative. However, the sudden increase in weight is suggestive of an approaching toxemia. She is told to take a tablespoonful of Epsom salts in water after returning home and to take the same dose morning and evening of the next day. Meat, fish, eggs and salt are eliminated from her diet and her fluids are restricted to 4 glasses of water daily. She is told to return in two days and to telephone at once if she has any headaches, blurring of vision, double vision, specks before the eyes, abdominal pain or increase in the swelling of her face, hands or feet.

She returns in two days and looks slightly improved. There is less facial and dependent edema and she has lost 3 pounds. The blood pressure has risen to 150/96. The urine is more concentrated, but it still contains no albumin. However, the hypertension is sufficient to alarm me and I tell Mrs. R. that I want her to enter the hospital that day so that we may treat her more thoroughly and observe her constantly. She wants to know if it will not be satisfactory to carry out the same policy at home. She is informed that this cannot be done and that her interests and those of the baby demand the best possible care. She says that she must confer with her husband and will let me know her plans later in the day.

After she has left the office I call her husband on the telephone and discuss the situation. I describe to him briefly the nature of eclampsia and tell him that it is practically a

preventable disease but that I must have his and Mrs R's cooperation if I am to take the responsibility. He informs me that I may count on them both and she enters the hospital that evening.

When the patient is admitted she is put to bed and is not allowed up until it is so ordered. A catheter specimen of urine is obtained for examination and a blood sample for the determination of the nonprotein nitrogen, urea nitrogen and the uric acid. The first day she is given nothing by mouth but 600 cc of water. The next day a milk diet is begun to the extent of 800 calories, which is gradually increased up to 1600 calories. The fluid output, including liquid feces, is measured. In no event is the fluid intake allowed to exceed the output. Immediately on entrance 1 ounce of a 50 per cent or saturated solution of magnesium sulphate is given by mouth and is repeated every hour unless the patient is asleep. This is continued until there are from 12 to 13 watery stools a day after which the frequency of the dosage is reduced. Few women whose bowels are moving freely develop eclampsia.

The limitation of fluids and the vigorous catharsis produces a marked reduction in the edema so that Mrs R loses 8 pounds more. Her face is less puffy and the pitting edema over her ankles has largely disappeared. The blood examination shows N P N 30.00, B U N 14.00, U A 4.00, which is not remarkable. The blood pressure falls the day after admission to 130/90 and remains in that general vicinity. There are no headaches, visual disturbances or epigastric pain. The urine, which becomes quite concentrated, shows a trace of albumin and the sediment reveals hyaline and granular casts with occasional red blood corpuscles. The amount of albumin varies from day to day, but is never less than a slight trace.

It is evident that Mrs R's condition has improved since entering the hospital but that she has not completely recovered, nor is she sufficiently improved to permit her return home. There seems to be no immediate danger of convulsions, but since preeclampsia is followed in a considerable number of cases by permanent vascular hypertension we must consider the advisability of terminating pregnancy. The child is practically mature, being within the last two weeks of pregnancy and there is no cephalopelvic disproportion. Exam-



ination shows the portio vaginalis to be effaced and the os one fingertip dilated. Accordingly, Mrs R is given 2 ounces of castor oil early in the morning and an enema two hours later. Her membranes are then ruptured artificially under strict aseptic precautions. Within an hour uterine contractions have begun and the delivery of a normal infant weighing  $6\frac{1}{2}$  pounds occurs in the evening.

Mrs R's subsequent course is uneventful. Her blood pressure falls after delivery to 120/74. A catheter specimen of urine a week postpartum contains only the slightest possible trace of albumin and the sediment is negative. A similar specimen on discharge from the hospital contains no albumin. When she was seen six weeks and six months after delivery her condition was normal in every way.



CLINIC OF DRS WILLIAM E LADD  
AND LEROY D FOTHERGILL

CHILDREN'S HOSPITAL

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IDIOPATHIC ULCERATIVE COLITIS IN CHILDREN

**Definition.**—Idiopathic ulcerative colitis is a disease not only difficult to treat but difficult even to define adequately. The patients whom we would include under this title are those who suffer from a chronic bloody mucous diarrhea, and who show ulcerative lesions in the colon for which no etiologic factor can be found. The disease may be mild or severe. It occurs most commonly in early adult life but is not infrequently found in the first twelve years of life, and it is with this age group that this paper is concerned.

**Etiology.**—In our opinion the etiology of the disease is still unsettled. Numerous theories have been advanced to explain it. The disease is generally believed to be of infectious origin. Numerous bacteria have at one time or another been considered to cause the disease. Barger has presented a good review of the literature, and the possible bacterial etiology of chronic ulcerative colitis, and described a diplococcus known by his name as the causative organism. We do not feel that the evidence is sufficient to accept the Barger diplococcus as the cause of the disease.

Twenty three of the patients of our series have had a detailed bacteriologic study. Cultures were taken from stools and also in many instances directly from ulcerations at the time of proctoscopic examination. The study of these cultures has not shown the consistent presence of any one organism to which pathogenic significance could be attached.

The Barger diplococcus was isolated in 8 instances and a late lactose fermenting organism, similar in its other cultural characteristics to the paratyphoid group, was isolated

from 2 patients In 1 patient cultures taken directly from the ulcers showed a hemolytic streptococcus and a Bagen diplococcus

**Pathology**—The ulcerative process of the colon in this disease is of characteristic appearance though subject to variation in amount and extent of distribution It commonly involves the rectosigmoid segment and descending colon but may be extended to the whole colon and an occasional case has been reported in which the lower portion of the ileum was also involved The ulcerations are typically small and placed close together leaving very little mucous membrane unaffected, and giving in the gross a red granular appearance rather than widely separated individual ulcers As the disease progresses the ulcerations extend to the deeper layers of the colon, replacing the muscle layers with scar tissue or eventually, at times, penetrating all layers and resulting in perforation and localized abscesses or peritonitis The remote systemic findings consist in general emaciation, loss of weight, and in cases of long standing, a secondary anemia which may be of considerable severity One or two of our patients have presented bizarre skin lesions and joint changes

**Symptoms**—The onset of the disease in children is usually insidious, although occasional cases may have an abrupt onset Usually the first symptom noted is a gradually increasing frequency of bowel movements These are often accompanied by cramps and abdominal discomfort As time goes on the bowel movements become more frequent and mucus, often in considerable amounts, appears in the stools Later, when numerous ulcers have appeared, the stools contain considerable pus and blood in addition to mucus The number of watery bowel movements containing these abnormal elements usually varies from five to fifteen daily, although in some patients they may be much more numerous Many such patients run a low grade fever although some may have normal temperatures Because of the almost continuous loss of blood in the stools, the symptoms and blood changes of a moderately severe anemia are found

The symptoms may continue unabated or with periodic remissions, for months or even years, during which time marked structural changes are occurring in the colon Such patients

lead a very depressing and miserable existence. The more severe cases may be confined to bed. The less severe cases, while not bedridden, become social outcasts. They are unable to attend school or engage in the usual play of their associates because of the embarrassing frequency of bowel movements.

As the disease continues the nutritional state of the patient becomes increasingly poor. A great deal of weight is lost and marked retardation in growth and development occurs. There is usually fairly good compensation for the disturbances in water and electrolyte metabolism. This is probably because of the chronicity of the disease.

**Physical Examination.**—On general physical examination of these patients with idiopathic ulcerative colitis one does not find any definite characteristic except the general emaciation due to the wasting process and the pallor due to the secondary anemia. Occasionally on abdominal examination tenderness is elicited by pressure along the course of the colon. Proctoscopic examination in contrast to the general examination is quite characteristic. When the proctoscope is introduced one will see first a considerable amount of grayish, mucopurulent material. When this is washed or gently wiped away the mucous membrane appears red and granular with minute ulcerations diffusely scattered over its surface. The mucous membrane bleeds easily on very slight trauma. Perhaps the most striking characteristic of the proctoscopic examination is the fact that one sees almost no normal appearing mucous membrane in contrast to other types of ulcerative colitis.

**Laboratory**—x Ray examination of a barium enema shows a characteristic change from the normal as soon as structural change has taken place in the colon. Early in the disease the haustral markings become shallow and infrequent, and later in the disease are entirely absent, giving what is usually described as a pipelike appearance. The bacteriologic findings in the stools will be considered as a part of the differential diagnosis.

**Diagnosis**—The diagnosis of idiopathic ulcerative colitis is suspected in any patient with a history of chronic bloody mucous diarrhea who presents a characteristic picture on proc-

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Tuberculous enteritis usually involves the upper end of the large bowel or terminal ileum, and may be demonstrated by x ray examination. Direct smears of fecal material, concentrated by antiformin, should be examined, and with negative results, such material should be injected into one or more guinea pigs.

A true chronic bacillary dysentery is extremely rare in children, at least in our experience. It is ruled out by the repeated culturing of fresh fecal material. It should be emphasized that a number of stool cultures are necessary. A single negative culture is of no value whatever. Agglutination reactions with the patient's serum and a large number of stock antigens are of value. A large group of antigens should be used because there are so many serologically different strains of dysentery bacilli. In our own agglutination studies we use, in addition to the dysentery antigens, a number of different strains of organisms belonging to the paratyphoid group.

The symptoms presented by patients with a Meckel's diverticulum may, in an occasional instance, be confused with those in early cases of chronic ulcerative colitis. In the former disease bleeding into the bowel is not uncommon and occasionally diarrhea may be present. In such patients, changes in the colon are not demonstrable by x ray following a barium enema and ulcers are not visualized at proctoscopic examination.

When a patient is admitted to this clinic with a history suggesting chronic ulcerative colitis the plan of diagnostic study carried out is as follows: the patient is kept at complete rest in bed and is given a low residue diet. The usual routine examinations such as complete physical, blood, and urinalysis are done. If the patient is febrile, one or more blood cultures are taken. Blood is also taken for a Wassermann reaction and for serum for agglutination with these antigens, B dysentery Shiga, B dysentery Flexner, B dysentery Hiss-Russell, B dysentery Sonne, B paratyphosus A, B paratyphosus B, B enteriditis, and B abortus.

Several freshly passed stool specimens (4 or more) are examined for the presence of *entameba histolytica* for the cysts of this parasite as well as being cultured for genic organisms.

toscopic and x-ray examinations and after other conditions have been eliminated by suitable bacteriologic studies

There are several conditions which have to be considered in the differential diagnosis. In children the most important conditions to be considered are amebic dysentery, tuberculous enteritis, chronic bacillary dysentery, and rarely Meckel's diverticulum. The acute diarrheas such as those caused by the dysentery bacillus and certain members of the paratyphoid group of organisms are seldom confused with chronic ulcerative colitis because of their acute onset and relatively short duration. Diarrhea associated with certain deficiency diseases such as pellagra, beriberi, or sprue should be considered through taking a detailed dietary history and seeking other clinical evidences of these disturbances. Malignant disease, diverticulitis, and polyposis are rarely seen in children and therefore do not as frequently offer a problem in differential diagnosis as in adults. Since the etiology and pathogenesis of chronic ulcerative colitis is not clearly understood, it is very important to exclude the above conditions before arriving at its diagnosis. In part, the diagnosis is arrived at by a process of elimination.

Amebic dysentery can be ruled out only by the careful examination of a considerable number of stool specimens by someone familiar with the appearance of both the cysts and vegetative forms of *Entamoeba histolytica*. It should be emphasized that to be of value, stool examinations for ameba should be done as quickly as possible after the stool is passed. Furthermore, at the time of proctoscopic examination of a patient suspected of ulcerative colitis, material should be taken directly from the ulcers and examined immediately for amebae. In occasional cases with a suggestive history, such as residence in the tropics, but with repeatedly negative stool examinations for amebae, it may be worth while to treat the patient with some emetine preparation as a therapeutic trial.

The tuberculin test is of great value in the differential diagnosis of tuberculous enteritis in children. If this test is negative to the larger doses of tuberculin (i. e., an intracutaneous injection of 1 mg.) it is reasonably certain that the enteritis is not of tuberculous origin. However, if the reaction is positive, a detailed and careful study is necessary



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When a patient is admitted to this clinic with a history suggesting chronic ulcerative colitis the plan of diagnostic study carried out is as follows: the patient is kept at complete rest in bed and is given a low residue diet. The usual routine examinations such as complete physical, blood, and urinalysis are done. If the patient is febrile, one or more blood cultures are taken. Blood is also taken for a Wassermann reaction and for serum for agglutination with these antigens, B dysentery Shiga, B dysentery Flexner, B dysentery Hiss-Russell, B dysentery Sonne, B paratyphosus A, B paratyphosus B, B enteriditis, and B abortus.

Several freshly passed stool specimens (4 or more) are examined for the presence of *entameba histolytica* and for the cysts of this parasite as well as being cultured for pathogenic organisms.

Intracutaneous tuberculin tests are done starting with 0.01 mg of tuberculin. If the reactions are negative to the smaller doses, the dosage is increased to 1 mg of tuberculin. If the tuberculin reaction is positive a thorough search is made by roentgen ray for any parenteral focus of infection. Stool specimens are carefully examined for tubercle bacilli by the methods described above.

The colon is examined by roentgen ray following a barium enema in order to appraise the amount, location, and characteristics of any structural change that may be present.

The child is finally subjected to proctoscopic examination (under anesthesia) in order to visualize any ulcers that may be present. At this time material is swabbed directly from the ulcers for smear examination, ameba search, and cultures.

The diagnosis of idiopathic chronic ulcerative colitis is arrived at only after all the data from such a study has been collected.

**Treatment**—After a diagnosis of idiopathic ulcerative colitis has been reached the question of what form of treatment should be employed naturally arises. On this subject there is little uniformity of opinion at the present time either as regards the general principles or the details. This situation has arisen for two reasons, one that there is a wide variation in the severity of the disease and, two, that in the more severe types of the disease no form of treatment is uniformly successful or curative. Broadly speaking, medical treatment is employed for a limited period of time for those patients in whom the diagnosis is doubtful or in whom the disease is mild and has been present for a short time only. The medical treatment consists of rest and general good hygiene. The patient is placed on a low residue diet containing an adequate amount of the essential vitamins. If the secondary anemia is marked it is combated by a soluble form of iron and transfusions. The use of opiates to control diarrhea is of doubtful wisdom on account of the chronicity of the condition. Such drugs as bismuth subnitrate or subcarbonate have been found to be of little value in our experience. Colonic irrigations are not of value, are painful, and must be dangerous on account of the possibility of causing perforation if the disease is of long duration. Autogenous vaccines made either from cultures of

the Bagen diplococcus or other organisms isolated from the feces of these patients have been of no therapeutic value in our experience. The use of a serum would seem somewhat illogical until such time as the causative organism has been proved beyond peradventure.

The question of the indications for surgical treatment and what form of operation should be done is again one that lacks uniformity of opinion. It is our belief that the unpleasantness of the operation has in most instances caused an unwarranted delay in its adoption. This delay has removed any possibility of curing the disease. We believe that the almost universal prolonged persistence of medical treatment of one form or another accounts for part of the usual pessimistic surgical point of view. There are two logical reasons for resorting to surgical treatment. The first is to save the life of a patient who is going downhill rapidly during the course of the disease. The second is to limit the progress of the disease and improve the patient's general condition, removing him from a state of chronic invalidism. The operation which we advocate for fulfilling these reasons is transverse ileostomy with complete external diversion of the fecal stream. We have had no experience with appendicostomy, cecostomy, or colostomy, but feel that there is not sufficient evidence of their merit in the literature to warrant their employment. It cannot be claimed that ileostomy is a pleasant operation or that it can be performed without risk. It can be claimed, however, that it is at times a life-saving procedure and that the inconvenience and drawbacks of an ileostomy are less than those of the disease.

There have been 26 patients treated at the Children's Hospital on whom a diagnosis of chronic ulcerative colitis has been made. Of these 26 patients 10 have received medical treatment only. Three of these 10 in whom the symptoms were rather mild and of short duration, have apparently recovered and stayed well for variable periods of time. Whether they will later have remissions is a matter of surmise. The other seven still have the disease and have not been improved by the various forms of treatment used, including autogenous vaccine therapy. The remaining 16 patients have all had medical treatment without improvement for periods of several

months to several years before resorting to surgical treatment. There are two exceptions to this statement in the cases of two infants who will be referred to presently.

Though the results of the surgical treatment in this series are far from gratifying, still there are features in the series which are hopeful and which lead to the belief that the results may be improved.

All of these 16 patients have had an ileostomy performed. Four who had had the disease from five to two years before operation, had the ileostomy closed, in one instance eight years later and in the other three about two years after ileostomy. These 4 patients have been followed afterwards for four years and eleven months, three years and nine months, two years, and one year and two months respectively. They were all having normal stools, were in good general condition and so far as we could gather, were, for the time being, well. Whether they will eventually have remissions is, of course, impossible to say. Perhaps of more significance than these 4 cases is the history and unfortunate end-result in a boy who had an ileostomy performed when he was nine years and ten months old. This boy had a history of bloody mucous diarrhea for over seven years, not as severe as in some of the other patients, but increasing in severity during the six months prior to the ileostomy. He had 6 to 8 stools daily with blood and mucus, and he was losing weight. The proctoscopic examination revealed the characteristic ulcerations, and barium enemas given at six-month intervals showed increasing structural change of the colon. Subsequent to the ileostomy he improved rapidly, gained 17 pounds in weight in the first six months, went to school, indulged in active exercise, and in short, lived a very normal life. At the end of two years, closure of the ileostomy was being considered when he developed a volvulus of the jejunum with acute intestinal obstruction from which he died. The notes of the postmortem examination of the colon are of interest. Gross examination, "The mucosa of the colon appears to be practically normal except for a very fine roughening of its surface. It is not injected and there are no areas of ulceration. Hanging from the serosa of the colon are a number of small appendices epiploicae." Microscopic examination of the colon. "There is a single layer of

columnar epithelium over practically the entire surface of the colon. The mucosal surface is remarkably smooth. The glands are rather small, but their epithelium is remarkably well preserved. The tunica propria is infiltrated with a moderate number of large and small mononuclear cells and a few polymorphonuclear leukocytes. There is slight congestion here also. The solitary follicles are markedly depleted of lymphocytes and infiltrated moderately by large mononuclear cells. There are fairly numerous small areas of necrosis just under the intact epithelial surface. One healed ulcer now covered by epithelium is noted." The pathologist, Dr. Farber, comments, "The findings here are of great importance in reference to the efficiency of the rest treatment of the colon by surgical means. Certainly there was no evidence of an active ulcerative colitis at the time of autopsy."

Besides the 4 patients who had the ileostomy closed and were at the last report apparently well, there are 5 patients in this series who have the ileostomy still open. One boy who had had the disease since he was ten years old, had an ileostomy at fourteen years of age. He was very emaciated, weak, confined to bed, and in very poor general condition. Following the ileostomy his condition improved markedly. He gained weight, was able to be up and lead a fairly normal life. Three years later proctoscopic examination revealed an active process in the colon. This patient may be a candidate for colectomy. He is not a candidate for closure of the ileostomy. Another patient who had had the disease only eight months when the ileostomy was performed, had a rather stormy course for a few weeks following operation, but at last note, eighteen months later, was in excellent condition. This patient may be able to have the ileostomy closed later. A third patient, a girl, contracted the disease at the age of eight, and the ileostomy was performed four years later, when she was in very poor condition. During her convalescence she developed a very extensive ischio-rectal abscess. Examination two years later showed the patient in excellent general condition. We believe the ileostomy in this instance was a life-saving procedure, even though the disease is still present. Proctoscopic examination at this time revealed some mucopurulent discharge, a mucous membrane that bled on very slight trauma,

one small polyp, and an anal sphincter of doubtful competence. We believe this girl should have a colectomy. Two other patients in this series acquired the disease in the first year of life. Prior to the appearance of the disease in these two infants we were not aware that it ever occurred at such an early age. In both instances a very careful study was made to see if there were not some other etiologic factor and in neither case was any found. Both infants had very careful medical care and ileostomy was resorted to only when a fatal outcome seemed imminent. In both instances great difficulty was experienced in maintaining adequate body fluids, both before and after ileostomy. The continuous introduction of saline solution intravenously proved to be very helpful and was continued for more than a week in both patients. The older of the two, who was seven months when the ileostomy was performed, was in good condition at the age of two years except for a slight rectal stricture which dilated readily. We believe this ileostomy can be closed soon. The younger of the two infants has had the ileostomy for seven months and is in good health at the present time. It is still too early to hazard a guess about the closure of the artificial opening.

There have been 7 deaths in this series of 26 cases, some directly attributable to the disease or its treatment and some of doubtful connection. One case has already been mentioned, the boy who did well for two years and then acquired a volvulus of the jejunum and died of intestinal obstruction. Another boy of thirteen who had the ileostomy performed in the seventh year of the disease, did exceptionally well for six months afterward. He had gained 40 pounds in weight when he developed carcinoma of the transverse colon, from which he died. A girl of nine years died of multiple perforations of the colon and peritonitis a week after she had the ileostomy performed. A boy nine years old who had had the disease over three years, died of perforation one month after ileostomy had been done, and another who had been followed medically at the Children's Hospital, died a few days after an ileostomy had been performed in another hospital. One patient who had done well for two years after the ileostomy, had a streptococcus infection of the wound following the operation for closure, and died, it was believed, of a streptococcus peritonitis. The

seventh patient died following an ileostomy and was found to have an ileitis as well as chronic ulcerative colitis at the postmortem examination

**Impressions**—It is doubtful whether conclusions are justified from so small a series of cases, but we have several definite impressions

- 1 The cause of the disease is still unknown
- 2 Diagnosis of idiopathic or chronic ulcerative colitis without careful bacteriologic, x ray, and proctoscopic examinations is not warranted
- 3 The disease has varying degrees of severity
- 4 We regard the idea expressed by McKittrick and Miller that ileostomy should be considered a permanent condition, as slightly too pessimistic to apply to our age group
- 5 Ileostomy is at times a life-saving procedure and is followed by rapid and lasting improvement in symptoms
- 6 We believe ileostomy should be performed before too much structural change has taken place, if we are to avoid the artificial opening being permanent.

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### THE CLINICAL SIGNIFICANCE OF PROBLEMS OF AB- SORPTION IN THE HUMAN GASTRO-INTESTINAL TRACT

It is becoming increasingly evident that diseases due to nutritional deficiency may occur even when the diet seems to be adequate. Materials valuable to the body may be lost, for example, by hemorrhage from any part of the body, or by loss through the kidneys owing to disease of these organs. During growth, pregnancy, and in other conditions such as fever or hyperthyroidism, in which increased demands are made upon the body stores for necessary materials, dietary deficiency disease may result if the increased demands are not met by an adequate supply of substance derived from the food. In such conditions as sepsis, cancer and dysfunction of certain organs, necessary material, though present in the body, may not be properly utilized. The diet, moreover, may be quite adequate for a normal person, but because of an insufficient secretory mechanism in the gastro-intestinal tract, substances may not be made available for the body. Castle has demonstrated how such a mechanism may be productive of Addisonian pernicious anemia. In this disease there is a deficiency of an enzyme-like substance in the gastric juice, the presence of which, in normal individuals, produces by the interaction with certain materials of the food a specific substance necessary for normal blood formation. Lastly, the diet may be adequate, but because of various gastro-intestinal abnormalities with or without diarrhea, food substances may not be absorbed and therefore not reach the body itself. Minot, Strauss and

Cobb<sup>1</sup> have summarized the trend of knowledge regarding these factors in deficiency disease as follows "One must also recognize that dietary deficiencies can develop because of disorders of the gastro-intestinal tract Necessary material may not be properly elaborated because of a lack of gastro-intestinal secretions, as occurs in pernicious anemia, or nutritious elements may be absorbed unsatisfactorily, leading to a state of deficiency exactly as if an insufficient amount of proper food had been ingested"

The study of the normal mechanism of intestinal absorption has been pursued intensively by physiologists for many years Physicians, moreover, have been aware for a long time of the importance of absorption in various aspects of medicine, for example, in the principle of the administration of cathartics, or in the choice of giving medicinal substances parenterally rather than orally The presence of good teeth for mastication, and adequate preparation of the food by cooking have been long recognized as important factors for the assimilation of food It is only recently, however, that the influence of absorption upon the causation of disease has attracted interest It is timely, therefore, to summarize our conceptions of the pathologic physiology of absorption, to indicate the position it takes in clinical medicine, and to outline methods of clinical study and of treatment

**The Mechanism of Intestinal Absorption**—"Absorption" refers to the transfer of substances across the membrane of the intestine, so that they are made available to the body as a whole Ingested substances are, for all practical purposes, still outside the body until they have passed the intestinal barrier The preparation of food substances for absorption by the action of the various secretions of the digestive organs is, of course, intimately linked with the process of absorption itself It is therefore obvious that impairment of the gastro-intestinal secretory mechanism and the absorptive mechanism may be difficult to separate clinically, and it is reasonable not to attempt to differentiate them too dogmatically

In order to approach the problem of intestinal absorption in its relation to disease it is necessary to consider the normal mechanism of absorption There seem to be innumerable fac-

tors which have to do with the absorption of substances in the intestine. *The nature of the substance itself* is of importance its concentration and mass, state of dispersion, hydrogen ion concentration, lipid solubility, surface tension, and then also such factors as the nature of accompanying substances and of the external secretions of the gastro-intestinal tract. *The character of the bowel wall* is to be considered the surface area (to which the number of villi contribute), the mechanisms of segmentation and peristaltic movement, the intra intestinal pressure, the movements of the villi, the permeability of the intestinal wall, the blood flow in the capillaries, the so-called "vital" selective ability of the lining cells. The subject has been reviewed in detail by Goldschmidt<sup>2</sup> and Magee,<sup>3</sup> and one draws the general conclusion from their work that, although physicochemical laws, in particular those of osmosis, can explain only a part of the phenomena of absorption, the apparently selective ability of epithelial cells may eventually be explained as physicochemical knowledge progresses. The factors governing normal absorption in the intestine being so numerous, it can readily be seen how complex may be the physicochemical states which modify absorption when the intestine is altered pathologically.

Certain substances are absorbed more easily than others from the intestine. Iron and the materials potent in pernicious anemia and pellagra are substances which apparently are not absorbed with ease, as is suggested by the great discrepancy between effective dosage when these substances are given by the parenteral route as opposed to the oral route. It seems possible that vitamins are likewise absorbed with relative difficulty and that this may explain the development of syndromes associated with deficiencies of these substances when the intestinal mechanism is disturbed although the diet is complete.

**Clinical Evidence of Malabsorption as a Cause of Disease**—Whereas there is abundant clinical evidence of disease which seems to be directly or indirectly the result of malabsorption, the concept is only with great difficulty amenable to scientific proof. One must first of all be assured that the dietary intake has been adequate. This evidence is frequently lacking, or is very difficult to obtain. Since disorders of the gastro-intestinal tract are accompanied almost invariably by

poor appetite, the actual rôle of impaired intestinal function is often very doubtful. However, examples are so numerous in which impaired intestinal absorption is either quite clearly or with great probability a factor in the development of nutritional deficiency, one is forced to regard it of importance. Diarrhea is perhaps the simplest example. When diarrhea and excessive intestinal motility are present, not only are food substances but also substances secreted into the intestinal lumen lost to the body. Thus, water, salts, protein, carbohydrate and fat are lost to the body and the loss of each may give rise to distinct clinical manifestations. From this simple example, it is illustrative to pass to that of idiopathic steatorrhea, which has been well described by Bennett, Hunter, and Vaughan.<sup>4</sup> In idiopathic steatorrhea, the bowel is anatomically as well as functionally deranged, there is protracted diarrhea, and the patient may suffer from multiple deficiencies: there may be low blood calcium, tetany and decalcification of the bones, low plasma proteins with edema, peripheral neuritis or evidence of other vitamin deficiency, and the blood may show the characteristics and the response to treatment of both pernicious anemia and iron-deficiency anemia.

Perhaps the most interesting examples in which disorders of the gastro-intestinal tract condition disease are in the fields of vitamin, protein, and mineral deficiency. Keefer,<sup>5</sup> among other investigators, has outlined examples in which keratomalacia, beriberi, scurvy, pellagra, rickets, tetany, osteoporosis and edema disease, either singly or combined, developed during the course of gastro-intestinal disease. He concluded that "it is evident that these conditions are observed not only following restricted diets, but also when pathological processes interfere with nutrition." Keefer and his coworkers<sup>6</sup> also observed that anemia was more common in pulmonary tuberculosis when diarrhea was present than when it was not. Urmey and others<sup>7</sup> reported beriberi with probably other deficiencies in a patient following an entero-enterostomy. Various deficiency states, producing such signs as corneal ulcers and peripheral neuritis, may occur in the course of ulcerative colitis.<sup>8</sup> Mackie and Pound<sup>9</sup> found evidence of deficiency states in 63 per cent of 75 cases of chronic ulcerative colitis, although a history of defective dietary was seldom elicited.

There is clear-cut evidence of poor absorption as an etiological factor in some forms of anemia. Castle and Rhoads<sup>10</sup> have considered malabsorption as an important factor in the anemia of many cases of sprue which may either be hypochronic (iron deficiency) or macrocytic (pernicious anemia). In sprue, large amounts of liver extract administered by mouth may fail, but liver extract given parenterally may be effective.<sup>11</sup> A similar state of affairs has been demonstrated in certain cases of intestinal anastomosis,<sup>11</sup> intestinal stricture<sup>12</sup> and obstructing tumor of the small bowel.<sup>13</sup>

In types of chronic hypochromic anemia in women in whom there is achlorhydria, atrophy of the tongue papillae and sometimes dysphagia, malabsorption of iron from the food has frequently been considered to play an etiological rôle. In these patients, the response of the reticulocytes and of hemoglobin regeneration to iron therapy is usually less satisfactory than in patients with hypochromic anemia who have acid in the gastric secretion.<sup>14</sup> Certain ectodermal disorders in this condition, such as skin atrophy, pigmentation, falling of the hair, fissures about the mouth, fragile nails, atrophy of the tongue papillae and of the pharyngeal mucous membrane, may be related to dietary deficiency which may be brought about, among other ways, by improper absorption of necessary food factors other than iron.

**Factors in the Production of Intestinal Disease and Diminished Absorption.**—The defective gastric secretion and the glossitis, which are so commonly observed in various anemic states, are perhaps only a part of pathological changes of the gastro-intestinal tract as a whole. Pathological changes of the stomach and small intestine, seen in pernicious anemia, for example, lend themselves only with extreme difficulty to detection during life. Nevertheless, these anatomical alterations, in part detectable by gastroscopic examination, but usually appreciated only at postmortem, may hinder the optimal absorption of food substances.

In the presence of ulcerative colitis, tumors of the intestine or intestinal abnormality due to adhesions or operative procedures, the immediate cause of a disorder of the absorptive mechanism seems explainable. It is very difficult to understand, and indeed to study, the insidious changes that take

place in the bowel in the course of such diseases as sprue, pellagra, and Addisonian pernicious anemia Cowgill<sup>15</sup> considers that the presence of adequate amounts of vitamin B may be of great importance to the normal functioning of the intestinal tract An indication of the effect of restricted diet is reflected by the recent studies of Miller and Rhoads<sup>16</sup> They fed a modified canine-black-tongue-producing diet to swine and produced oral mucous membrane lesions, achlorhydria and a loss of the antipernicious anemia activity of the gastric secretion together with a blood picture which resembled that of pernicious anemia

Hasty conclusions are unwise in this difficult field It does not seem illogical, however, to consider that a vicious circle is common in many of the chronic deficiency states The vicious circle may be stated as follows inadequate dietary intake of certain necessary substances leads to anatomical or physiological changes within the intestine and then to diminished absorption of necessary substances, which in turn lead to further disorder of the intestinal function The factors of race, age, inheritance, changes of the glands of internal secretion, climate may all play a rôle in the etiology of particular kinds of gastro-intestinal disorders leading to deficiency disease The exact part which they play is impossible to define at the present time

#### **Methods of Clinical Study of the Rate of Absorption**

—The conditions affecting the normal rate of absorption being so many and varied, it is impossible to draw far-reaching conclusions from any one method of testing the rate of absorption Surgical operative measures, moreover, which are of great value in animal experimentation, are not open to the clinician, except by chance in rare cases Nevertheless, certain methods of clinical study have been in use Some of these methods are the glucose tolerance test which has been used in cases of chronic diarrhea, the study of the motility of the bowel,<sup>17</sup> the transference of weight to distant parts of the body after the ingestion of water,<sup>18</sup> the physiological effects of ingested drugs, allergic skin reactions to ingested protein,<sup>19</sup> and the rate of excretion of dyes in the urine<sup>20</sup> Singer and Wechsler<sup>21</sup> found that, when the galactose toler-

ance test was performed upon patients with anemia and achlorhydria, no galactose appeared in the urine

The author, working with Fullerton<sup>22</sup> studied a variety of cases in which it was thought that some disturbance of intestinal absorption might be present, including cases of achlorhydria with and without anemia, infections, cirrhosis of the liver, myxedema and scurvy. It was found that the ingestion of water and its excretion in the urine depended upon so many variable factors that it was not of value. The same was found true of the ingestion of glycine and the subsequent determinations of the amino-acid nitrogen content of the blood. Employing a method which has been used by Thienes and Hockett,<sup>23</sup> they administered 0.25 Gm. of potassium iodide in dilute solution and determined the time of the first appearance of iodine in the sputum. In normal individuals, iodine first appeared in the sputum in from ten to fifteen minutes. In most of the cases the time of the first appearance of iodine was delayed significantly. As the patients improved, the time of the first appearance shortened and approached or reached the normal time. The appearance time of iodine after the administration of potassium iodide intravenously, by means of which the influence of the intestine was avoided, was similar in normal subjects and patients. It was therefore believed that delay in the appearance of iodine in the sputum after the ingestion of potassium iodide was a rough measure of disturbance of intestinal absorption.

These methods of studying absorption may be classified as indirect and there are quite obvious objections to many of them. A new technic, which offers the possibility of studying the rate of absorption by a direct method in man has been presented by Miller and Abbott.<sup>24</sup> This technic, which makes use of multiple lumen tubes passed into any desired part of the gastro-intestinal tract seems to offer a distinct advantage over indirect methods. It cannot be considered of value for routine use but will undoubtedly help to unravel certain problems regarding human intestinal absorption.

**Treatment of Disordered Intestinal Function Inhibiting Absorption**—The advantage to be gained by a good method of testing the rate of intestinal absorption would be not only to detect diminution of the absorption rate in dis-

orders of the intestine, but also to aid in evaluating methods of treatment when such conditions existed. Very little, however, is accurately known of this subject. Recovery of the papillae of the tongue, improvement in the appearance of the mucosa of the stomach, and improvement of the appetite have been observed in various sorts of anemia associated with dietary deficiency following therapy with iron or liver extract. Spies,<sup>25</sup> among other physicians, has observed healing of mouth lesions and control of diarrhea in the treatment of pellagra with large doses of liver extract parenterally. Improvement of lingual changes and of diarrhea in sprue by the parenteral administration of liver extract also have been noted.<sup>10</sup> Such improvement is very likely associated with a definite return toward normal of the accompanying pathology or altered physiology of the intestine. Large doses of a deficient factor, if necessary parenterally, therefore, are indicated when disorder of the intestine is associated with nutritional deficiency. The aim should be to detect nutritional deficiency early and before permanent damage to the bowel results. By being alert, one may perhaps recognize subjects susceptible to such disorders of the gastro-intestinal tract which might lead to deficiency disease, and thus preventive measures could be applied which undoubtedly would accomplish the most. From our present knowledge, preventive measures would consist largely in the choice of an optimal diet adjusted nicely in respect to all its constituents, having in mind the health of the body as a whole and the gastro-intestinal tract in particular.

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